6.0 EPIDEMIOLOGY STUDIES

The existing epidemiology studies provide the most appropriate data from which to determine the relationship between asbestos dose and response in humans. As previously indicated, however, due to a variety of methodological limitations (Section 5.1) , the ability to compare and contrast results across studies needs to be evaluated to determine the confidence with which risk may be predicted by extrapolating from the "reference" epidemiology studies to new environments where risk needs to be assessed. This requires both that the uncertainties contributed by such methodological limitations and that several ancillary issues (identified in Chapter 2) be adequately addressed.

A detailed discussion of the methodological limitations inherent to the available epidemiology studies was provided in the Health Effects Assessment Update (U.S. EPA 1986) and additional perspectives are provided in this document (Section 5.1). The manner in which the uncertainties associated with these limitations are addressed in this document are described in Appendix A. As previously indicated (Chapter 2), the ancillary issues that need to be addressed include:

- whether the models currently employed to assess asbestos-related risk adequately predict the time-dependence of disease;
- whether the relative in-vivo durability of different asbestos mineral types affect their relative potency;
- whether the set of minerals included in the current definition for asbestos adequately covers the range of minerals that potentially contribute to asbestos-related diseases; and
- whether the analytical techniques and methods used to characterize exposures in the available epidemiology studies adequately capture the characteristics of exposure that affect biological activity.

All but the third of the above issues are addressed in this Chapter. Currently, the third issue can best be addressed by evaluating inferences from the broader literature (see Chapter 7). The remaining issues are addressed separately for lung cancer and mesothelioma following a brief overview of the approach adopted for evaluating the epidemiology literature.

6.1 APPROACH FOR EVALUATING THE EPIDEMIOLOGY LITERATURE

To develop dose/response relationships (and corresponding risk coefficients) for use in risk assessment from epidemiological data, two basic types of information are necessary: information on disease mortality in the study population (cohort) and information on the asbestos exposure experienced by each member of the cohort. So that disease mortality attributable to asbestos can be distinguished from other (background) causes of death, it is also necessary to have knowledge of the rates of mortality that would be expected in the study population, absent exposure. Normally, such information must be determined based on a "reference" or "control" population.

Ideally, one would like to have complete knowledge of exposure at any period of time for each individual in the cohort and complete access to the data in order to fit different types of dose/response models to the data so that the approach for evaluating the relationship between dose and response can be optimized. In most instances, unfortunately, the data suffer from multiple limitations (see Section 5.1 and Appendix A) and the epidemiologist is further constrained by less than complete access to the data.

Briefly, the major kinds of limitations that potentially contribute to uncertainty in the available epidemiology studies (and the effect such limitations likely produce on trends in potency estimates) include:

- limitations in the manner that exposure concentrations were estimated (likely increases random variation across studies);
- limitations in the manner that the character of exposure (i.e. the mineralogical types of fibers and the range and distribution of fiber dimensions) was delineated (likely increases systematic variation between industry types and, potentially, between fiber types);
- limitations in the accuracy of mortality determinations or incompleteness in the extent of tracing of cohort members (likely increases random variation across studies);
- limitations in the adequacy of the match between cohort subjects and the selected control population (likely increases random variation across studies and may have a substantial effect on particular studies); and
- inadequate characterization of confounding factors, such as smoking histories for individual workers (likely increases random variation across studies and may have a substantial effect on particular studies).

More detailed discussion of the above limitations is provided in Section 5.1. The manner in which these limitations are being addressed in this evaluation are described briefly below and in more detail in Appendix A.

The existing asbestos epidemiology database consists of approximately 150 studies of which approximately 35 contain exposure data sufficient to derive quantitative dose/response relationships. A detailed evaluation of 20 of the most recent of these studies, which includes the most recent followup for all of the cohorts evaluated in the 35 studies, based on the considerations presented in this overview, is provided in Appendix A.

Importantly, this new analysis of the epidemiology database differs from the evaluation conducted in the 1986 Health Effects Assessment Update (U.S. EPA 1986). Not only does it incorporate studies containing the latest available followup for the exposure settings previously evaluated and several additional studies addressing new exposure settings, but the manner in which the analysis was conducted incorporates important, new features. These new features include:

- estimation of more realistic confidence bounds for the dose-response factors derived from each study; and

- for the lung cancer model, introducing a parameter, "α", which represents the ratio of the background rate of lung cancer in the cohort relative to the control population.

Confidence bounds were adjusted to account for uncertainty contributed by the manner that exposure was estimated, by the manner that work histories were assigned, and by limitations in the degree of followup, in addition to the traditional practice of accounting for the statistical uncertainty associated with the observed incidence of disease mortality. Thus, most of the major contributors to the overall uncertainty of each study are now addressed, at least in qualitative fashion. A detailed description of how the new confidence bounds were constructed is provided in Appendix A.

Note, in the text of this Chapter, we occasionally refer to significant differences between certain measured or estimated values. When such differences are determined informally (for example, by comparing confidence intervals) they are simply referred to as "significant." When they are determined formally (by statistical test), they are denoted as "statistically significant."

In this analysis, dose-response coefficients were estimated for each cohort both by requiring that $\alpha = 1$ (the traditional approach) and by allowing α to vary while optimizing the fit of the data. Allowing α to vary addresses such potential problems as differences in the relative fraction of smokers among cohort and controls, respectively, or

differences in background cancer rates due to lack of the appropriateness of the selected control population for the cohort. As indicated in Appendix A, such adjustments have a substantial effect on the fit of the EPA model to the data for several specific cohorts and a corresponding effect on the estimates of the lung cancer dose-response coefficients for those cohorts.

To better evaluate the sources of variation in estimated dose-response coefficients observed across the available studies and potentially reconcile such variation so that the precision of asbestos risk assessments might be improved (Sections 6.2 and 6.3), we were also able to obtain the original, raw data for selected cohorts from a limited number of some of the most important of the published epidemiology studies. This allowed us to more formally evaluate the appropriateness of the existing U.S. EPA models for lung cancer and mesothelioma, respectively, and to evaluate the effects of such things as fiber biodurability. The models were evaluated by determining the fit of the models to various representations of the time-dependence of mortality observed in these raw data sets. A biologically based model, the two-stage model developed by Moolgavkar et al. (Moolgavkar and Luebeck 1990) was also fit to the observed time-dependence and contrasted with results from the U.S. EPA models.

Separately, we also completed an evaluation to consider questions concerning the appropriateness of the range of fiber sizes characterized in the published epidemiology studies and whether adjusted exposure indices might improve the quality of asbestos risk assessments.

6.2 LUNG CANCER

The Airborne Health Effects Assessment Update (U.S. EPA 1986) utilizes a model for lung cancer in which the asbestos-related age-specific incidence of lung cancer, "t" years from onset of exposure, is proportional to cumulative asbestos exposure at time t-10 years, multiplied by the age and calendar year incidence of lung cancer in the absence of asbestos exposure. A linear relationship between cumulative dose and response was assumed based on the ten epidemiology studies identified (in the 1986 EPA document) as containing sufficient information to establish a dose/response curve for asbestos induced lung cancer:

$$I_L = I_E[1+K_L \cdot f \cdot d_{(t-10)}] \qquad (6.1)$$

where:

"I_L" is the overall incidence of lung cancer (expected new cancers per year per person) adjusted for age and calendar year;

"I_E" is the corresponding cancer incidence in a population not exposed to asbestos;

"f" is the concentration of asbestos (expressed as PCM fibers longer than 5 µm in the existing evaluations of the published epidemiology data);

"t" is the time since onset of exposure in years;

"$d_{(t-10)}$" is the duration of exposure excluding the most recent 10 years; and

"K_L" is the proportionality constant between dose and response. This is the risk coefficient that represents the potency of asbestos.

The above model is a relative risk model in that it assumes that the excess incidence of lung cancer from asbestos is proportional to the incidence in an unexposed population. Since smokers have a much higher incidence of lung cancer, if smoking-specific incidence rates are applied, the model predicts a higher excess incidence of asbestos-related lung cancer in smokers than in non-smokers. This is consistent with the multiplicative relationship between smoking and asbestos that has been observed in epidemiological studies (see, for example, Hammond et al. 1979). Note that the K_L in the model pertains to an occupational pattern of exposure (e.g., 8 hours per day, 240 days per year) and must be modified before application to environmental exposure patterns.

Equation 6.1 is generally written as follows to indicate that K_L is a proportionality constant between dose and response:

$$K_L(f)(d') = RR-1 \qquad (6.2)$$

where:

"RR" is the relative risk and is equal to (I_L/I_E) and d' is now the duration excluding the final 10 years before observation of total lung cancer deaths.

6.2.1 The Adequacy of the Current EPA Model for Lung Cancer

Access to the raw epidemiology data from a small number of key studies allowed us to evaluate the adequacy of the EPA model for describing the time-dependence for lung cancer in asbestos exposed cohorts. For this analysis, the raw data for the cohort of crocidolite miners in Whittenoom, Australia was graciously provided by Nick DeKlerk (unpublished) and the raw data for the cohort of chrysotile textile workers (described by Dement et al. 1994) was graciously provided by Terri Schnorr of NIOSH. The Whittenoom cohort was originally described by Armstrong et al. (1988), but the data provided by DeKlerk included additional followup through 1999.

The EPA lung cancer model was fit to the raw data from both South Carolina and Wittenoom. In these analyses, each person-year of followup was categorized by cumulative exposure defined using a lag of 10 years, in accordance with the EPA lung cancer model. The data were then grouped into a set of cumulative exposure categories and the observed and expected numbers of lung cancers were computed for each category. For South Carolina, expected numbers were based on sex-race-age- and calendar-year-specific U.S. rates and separate analyses were conducted for white males, black males, and white females, as well as for the combined group. For Wittenoom expected rates were based on age- and calendar-year-specific rates for Australian men. These data were also categorized by cumulative exposure lagged 10 years. The resulting fit of the EPA model to the data from Wittenoom and South Carolina are presented in Tables 6-1 and 6-2, respectively.

The data in these tables were fit assuming that the observed cancers in each cumulative exposure category had a Poisson distribution with mean response equal to the expected response in the comparison population times α $(1 + K_L*CE_{10})$, where the linear slope, K_L, is the "lung cancer potency factor" in the EPA lung cancer model, and CE_{10} is the mean cumulative exposure for a category computed using a lag of 10 years.

For the Wittenoom data (Table 6-1), the fit with $\alpha = 1$ is poor ($p < 0.0001$), as the model overpredicts the number of cancers in the highest exposure category and greatly underpredicts at lower exposures. By contrast the fit of the model with α variable is adequate ($p = 0.1$). This model predicts a high background of lung cancer in this cohort ($\alpha = 2.1$) and a fairly shallow slope, with the relative risk increasing only from 2.1 at background to 3.6 in the highest exposure category. A test of the hypothesis that $\alpha = 1$ for this cohort is rejected ($P < 0.01$) and the model fit to the data (with α variable) predicts $K_L = 0.0047$.

The fit of the EPA model to the South Carolina lung cancer data categorized by cumulative exposure is shown in Table 6-2. The model with $\alpha = 1$ cannot be rejected both when the model is applied to white males only ($p = 0.54$) or with all data combined ($p = 0.92$). Since the values α and K_L estimated from white males only are similar to those estimated using the complete cohort (black and white males and white females), the fit to the complete data is emphasized in this analysis. This model fit to the data predicts $\alpha = 1.2$ and $K_L = 0.021$ $(f/ml\text{-}y)^{-1}$. A test of the hypothesis that $\alpha = 1$ for this cohort cannot be rejected ($P = 0.21$).

Table 6-1

Table 6-2

6.2.1.1 Time Dependence

The EPA model was next evaluated to determine whether it adequately describes the time-dependence of the mortality observed in the Wittenoom and South Carolina cohorts. The model predicts that relative risk will remain constant following 10 years from the time of last exposure.

Table 6-3, shows the fit of the EPA model to the Wittenoom data categorized by time since last exposure. In each category of time since last exposure, the number of lung cancer deaths are predicted by the EPA model using the parameter values calculated in Table 6-1, based on the expected cancers and the average cumulative exposure for each category. This categorization allows investigation of the assumption inherent in the EPA model that the relative risk remains constant following 10 years from last exposure. The Wittenoom data appear to be consistent with this assumption, as the excess relative risk per f/ml-y of cumulative exposure varies only between 0.059 and 0.073 for categories representing more than ten years from last exposure.

The conclusion that relative risk remains constant following 10 years from last exposure among Wittenoom miners is further illustrated in Figure 6-1. Figure 6-1 is a plot of the quantity: (relative risk - α)/(cumulative exposure) versus time since last exposure. Based on the modified form of the EPA model (in which α is allowed to vary), this quantity, $(RR-\alpha)/(CE_{10})$, should be constant and equal to $\alpha * K_L$ (beyond 10 years from last exposure). Figure 6-1 demonstrates that this is exactly the behavior observed among Wittenoom miners, where the value of the quantity plotted on the Y-axis rises rapidly until 10 years after exposure ends and then remains constant for all longer times. Moreover, a test of the hypothesis that the slope of the data depicted in Figure 6-1 (beyond 10 years after the end of exposure) differs from zero cannot be rejected

Because it has been reported that asbestos fibers (especially chrysotile but including amphiboles) dissolve in biological fluids and that animal studies suggest that the tumorigenicity of fibers is proportional to in-vivo durability (Section 7.2.4), the Wittenoom data categorized by time since last exposure was also fit to a modification of the EPA lung cancer model in which the cumulative exposure variable is replaced by an estimate of internal dose derived assuming first-order clearance of fibers. Results are presented in Table 6-4

In developing Table 6-4, a preliminary investigation, based upon an “exact” likelihood that did not involve categorization of exposures, indicated that this model provided a best fit using a half-life of 11 years and a lag of 12 years. As this table indicates, despite optimizing the model with respect to the lag and half-life, it did not fit the data as well as the standard EPA model based upon cumulative number of inhaled fibers. Thus, there is no evidence from the Wittenoom data that crocidolite fibers degrade (or

Table 6-3

Table 6-4

Figure 6-1

that the effects of crocidolite fibers are diminished) in vivo over time scales that are short relative to a human life time and this is consistent with the data presented in Section 7.2.4 that suggest crocidolite fibers likely last many decades in human lungs, at a minimum. It is also consistent with the appearance of Figure 6-1, which shows no decrease in the effect of crocidolite following cessation of exposure.

Table 6-5 shows the fit of the EPA model to the South Carolina data categorized by time since last exposure. This table was constructed in the same manner as Table 6-3. In contrast to the data from Wittenoom, the time dependence of the South Carolina data cannot be adequately fit with the EPA model, whether α is held equal to one ($P < 0.0001$) or allowed to vary ($P < 0.0007$). A plot of $(RR-\alpha)/CE_{10}$ versus time (Figure 6-2) indicates why.

In Figure 6-2 (as with the Wittenoom data), the quantity plotted on the Y-axis increases sharply to a maximum at approximately 10 years following the end of exposure. In contrast to what is observed for Wittenoom, however, the value of this quantity decreases with time beyond the first 10 years following the end of exposure. This decrease is clear from the figure, despite some scatter in the data. Thus, in contrast to the assumption inherent to the EPA model, relative risk decreases precipitously in this cohort after 10 years following the cessation of exposure. This suggests that the effects of chrysotile are somehow diminished after long periods of time.

There are several reasonable hypotheses that might explain the decrease in relative risk with time within the South Carolina cohort. Among those that have attracted interest is the possibility that risk is a function of biodurability (for example, see Section 7.2.4). We therefore decided to explore this possibility.

Given that the expected lifetime for respirable chrysotile fibers in biological fluids is anticipated to be only on the order of a year (see Section 7.2.4), further analysis of the decreasing trend observed in Figure 6-2 is warranted. Therefore, the South Carolina data were also fit using the modified form of the EPA model that accounts for internal dose (rather than cumulative exposure). In this model, as indicated above, the internal dose is derived from cumulative exposure, except it is assumed that, from the moment that a fiber is deposited in the lung, it dissolves by a first order process. Actually, the best analysis of the dissolution process indicates that it is likely zero order, but the first order decay (see Section 7.2.4) is assumed as an approximation because this provides an easier description of the lifetime of the material.

Table 6-5

Figure 6-2

Table 6-6 shows the fit to the South Carolina data to the EPA model using internal dose. This Table was derived from the South Carolina data in the same manner that Table 6-4 was derived from the Wittenoom data. Since data appeared to be about equally consistent with a range of lags and half-lives, for consistency, the same values were used as with the Wittenoom data. This table indicates that this model provides an adequate fit to the South Carolina data (P = 0.16).

Assuming a first order decay process, the best fit trend line to the data beyond 10 years following cessation of exposure in Figure 6-2 suggests a half-life for chrysotile of approximately 20 years. A similar analysis of the Whittenoom data suggests a half-life for crocidolite that is > 700 years, which is no different than infinity.

Although this is in stark contrast to the dissolution half-life for chrysotile fibers estimated based on in-vitro data, these results may not be inconsistent. There are at least two reasonable explanations for this apparent discrepancy. First, the data in Figure 6-2 track the risk attributable to the presence of chrysotile, not the presence of chrysotile itself. It is therefore reasonable that, even if the chrysotile fibers disappear readily, the risk from their initial presence may decay only much more slowly; the biological changes induced by the initial presence of the fibers may persist.

Second, as indicated in the in-vitro studies (see Section 7.2.4), the dissolution rate of chrysotile is limited by the rate at which fluid flows past the material. The maximum dissolution rate (i.e. the rate reported in the in-vitro studies) is observed only when flow is adequate. Otherwise, partial saturation of the solution surrounding the chrysotile fibers will slow the dissolution rate until it is only a fraction of what is observed in the optimally designed studies. Therefore, that a slower dissolution rate is suggested by the South Carolina data may simply indicate that the various biological compartments in which the biologically active fibers are located do not allow for adequate flow of an adequate reservoir of biological fluids to maintain the dissolution rate at its theoretical maximum.

An alternate hypothesis is that the fibers are not dissolving at all but are simply being sequestered in some manner that reduces their biological activity with time. Such a hypothesis, however, does not appear consistent with the animal data that suggests that tumorigenicity is indeed a function of the in-vivo durability of fibrous materials (see Section 7.2.4). However, other hypotheses may also reasonably explain the data. Therefore, although relative risk clearly decreases with time after cessation of exposure among the South Carolina workers and such observations are not inconsistent with the possibility that this is an effect of biodurability, it is premature to conclude such a link without further study.

Table 6-6

Importantly, the time-dependent behavior described above for crocidolite and chrysotile are each based on analysis of data from only a single study. Thus, although such trends are also consistent with additional evidence from animal studies and other implications from the literature, it would be useful to confirm these observations by analyzing additional raw epidemiology data sets. If they can be acquired, the raw data from Libby may serve as a second example for amphiboles and the lung cancer data from Quebec may serve as a second example for chrysotile.

6.2.1.2 Comparison with biologically-based model

To further evaluate the behavior of the EPA model, results were compared with those of a biologically based (two-stage) model.

Definition of the two-stage model. The two-stage model of cancer implemented in this report (Moolgavkar and Luebeck, 1990) assumes that there is a population of normal cells under homeostatic control whose size remains fixed at X. A normal cell mutates at a given rate to an intermediate cell. (Mathematically, intermediate cells are generated according to a non-homogeneous Poisson process with intensity v, which implies that the per-cell mutation rate is v/X. For a given value of v the hazard function does not depend upon X and, without loss of generality, X was fixed at 10^7 cells.) An intermediate cell divides into two intermediate cells at a rate α, dies at a rate β, and divides into one intermediate and one malignant cell at a rate μ. (Mathematically, a clone of intermediate cells is a non-homogeneous birth, death and mutation process.) Importantly, the "α" in this model is in no way related to the "α" variable used to adjust for background mortality in the EPA lung cancer model and the two should not be confused.

The mortality hazard function (rate of dying of cancer at age t among persons who survive to that age) is assumed to be the hazard for the occurrence of the first malignant cell, with a delay of L years. That is, the mortality hazard at t years of age is assumed to be h(t-L), where h is the hazard for the occurrence of the first malignant cell. Thus, L represents the delay between the occurrence of the first malignant cell and the subsequent death from the resulting cancer. Following the assumption of Doll and Peto (1978) and Moolgavkar *et al.* (1993), a lag of L = 4 years was generally assumed. We note that the lag in this model is conceptually different from the lag of ten years used in the EPA models. Whereas the lags in the latter model were empirically derived based on goodness of fit, the lag in the two-stage model has a mechanistic interpretation and, consequently, should not necessarily have the same value.

To introduce the effect of exposure to asbestos into the model, one or more of the parameters v, α, β or μ were assumed to be linear functions of the instantaneous whole-body fiber burden, d(t), where t indicates age:

$v(t) = v_0 + v_1 * d(t)$,

$\alpha(t) = \alpha_0 + \alpha_1 * d(t)$,

$\beta(t) = \beta_0 + \beta_1 * d(t)$,

$\mu(t) = \mu_0 + \mu_1 * d(t)$.

The hazard function, h(t) and the corresponding survival function (probability of surviving to age t without death from lung cancer in the absence of competing causes of death), $S(t) = \exp(-\int_0^t h(s)ds$, predicted by this model, although mathematically complex, can be solved for explicitly whenever the parameters are piecewise constant (Moolgavkar and Luebeck, 1990; Heidenreich *et al.*, 1997).

In application of this model to lung cancer (and mesothelioma) data from Wittenoom, South Carolina, and Quebec: the fiber body burden, d(t), was computed (up to a multiplicative constant) from a subject's exposure pattern, assuming a first-order elimination process with an elimination rate of r (half-life of -Ln(.5)/r). In these calculations, an average exposure rate during work hours was computed for each year of work. Based on the first-order assumption, the body burden at time t resulting from exposure to an average of f f/ml during the year between s and s+1 is

$$d(t) = (f/r)[1 - \exp(-r(t-s)] \quad \text{for } t \leq s+1$$
$$= (f/r)[1 - \exp(-r)]\exp[-r(t-s-1)] \quad \text{for } t > s+1.$$

This expression does not include the multiplicative constant needed to convert from the air concentration of asbestos to internal deposition rate, but without loss of generality is assumed to be included in the parameters μ_1, α_1, β_1, and v_1.

The average body burden between t and t+1 years due to exposure between s and s+1 years was computed by integrating this expression from t to t+1. The average body burden during each year was then computed by summing the contributions to the average from each year (by summing over $s \leq t$). The body burden d(t) was approximated by the step function formed by these yearly average body burdens. With this approximation the two-stage parameters v(t), $\alpha(t)$, $\beta(t)$ and $\mu(t)$ are piecewise constant and the exact solution to the two-stage model for this case (Heidenreich *et al.*, 1997) was used to calculate the hazard, h(t) and survival function, S(t). This calculation was made using a FORTRAN subroutine kindly provided by Drs. Suresh Moolgavkar and Georg Luebeck.

This model was fit to the raw lung cancer and mesothelioma data from Wittenoom and South Carolina, and to the raw mesothelioma data from Quebec using the method of maximum likelihood. The contribution to the likelihood for a subject who began work at age t_0 and died of cancer at age t_1 was $h(t_1)*S(t_1)/S(t_0)$, and the corresponding expression for a subject whose followup ended at t_1 without resulting in death from cancer was $S(t_1)/S(t_0)$. The complete likelihood was computed as the product of these individual contributions. The software program, MINUIT, developed by CERN in Geneva, was used to maximize the log-likelihood.

The full two-stage model described above has eight parameters (nine if the elimination rate, r, is included), which is too many to be estimated reliably using the epidemiologic data available. Moreover, the general model is not fully identifiable, as different combinations of parameters can lead to the same hazard (Heidenreich *et al.*, 1997). Accordingly, in applications of this model, not all of the parameters were estimated independently. For example, in most cases only one of the two-stage parameters (v, α, β, μ) was allowed to be dose-related. Also, to reduce the number of estimated parameters, in most cases either α or β was fixed at zero, because, when the mortality rate is low, h(t) is practically a function of the difference between these two parameters. Also, the elimination rate, r, was not estimated from the epidemiologic data, but was determined from evidence on the durability of different types of asbestos fibers (see Section 7.2.4).

Although the parameters in the two-stage model at least nominally represent physiological phenomena, it must be realized that the model is, at best, likely to be a highly idealized representation of a very complex process (see Section 7.3.1). Accordingly, the results from this model are probably best used to investigate the relative contributions to risk from exposures at different ages (e.g., if the model predicts that v is dose-related, then earlier exposures are more important in determining risk, whereas if the model predicts that μ is dose-related, then more recent exposures are more important). Moreover, if the model predicts that v is dose-related, the offending toxic substance can be considered to be acting as a classical initiator; if α (or, more precisely, α - β) is dose-related, the toxic substance is more likely a promoter. If μ is dose related, the toxin is likely a late-stage actor, which also would present different behavior than an initiator. An important advantage of the two-stage model is that, since it models risk as a function of internal dose, it can naturally incorporate consideration of fiber clearance.

Applying the two-stage model to lung cancer. Table 6-7 summarizes the results of three applications of the two-stage model to the lung cancer data from Wittenoom, and Table 6-8 summarizes a similar application of the model to the South Carolina lung cancer data. With each set of data, the model is fit allowing either v, α, or μ to be a linear function of the fiber body burden. In keeping with the half-life estimates based on the durability of chrysotile and amphibole fibers in Section 7.2.4, for the South

Table 6-7

Table 6-8

Carolina data, the half-life of internally deposited fibers was assumed to be 0.5 years (r = -ln(0.5)/20 = 1.39/year) and, for the Wittenoom data, the half-life was assumed to be 20 years (r = 0.035/year).

Note that these analyses were completed before the analysis of the time-dependence of the data using the EPA model, so that we did not have the opportunity to go back and run this biological model using half-lives that might better represent what has been observed with the time-dependence of the Wittenoom and South Carolina data (Section 6.2.1.1). However, now that we have developed an approach that allows evaluation of the time-dependence of lung cancer mortality based on estimates of internal dose using the EPA model, further analysis using the two-stage model may not be warranted (see Section 6.3.1).

When applied to the Wittenoom data the model provided comparable descriptions of the data (i.e., similar likelihoods) when either the proliferation rate of intermediate cells, α, or the mutation rate of intermediate cells, μ, was assumed to be dose related. These models provided a much larger likelihood than the model in which the mutation rate of normal cells, ν, was assumed to be dose-related. Note that the "likelihoods" reported in the table are "negative likelihoods" so that the smaller the number in the table, the larger the actual likelihood.

Table 6-9 shows the fit of the best-fitting 2-stage model to the Wittenoom data categorized by time since last exposure, compared to the fit of the EPA lung cancer model. As this Table shows, the simpler EPA model fits these data better than the 2-stage model, although the fit of both models is adequate (lack of fit p-value = 0.12 for 2-stage model and 0.35 for EPA model).

The above indicates that the best-fitting model runs for Wittenoom adequately describe the time-dependence for lung cancer and further indicate that asbestos primarily affects α (and potentially μ). This suggests that crocidolite may be acting primarily as a promoter (or at least a late-stage actor) rather than an initiator toward the induction of lung cancer, which is consistent with inferences from several recent in-vitro studies (Section 7.3.3.4 and 7.3.4.7) and a recent retrospective cohort study of retired workers (Sanden et al. 1992).

Table 6-10 shows the fit of the 2-stage model (in which ν, the mutation rate from normal to intermediate cells is dose-related, i.e. the best-fitting model) to the totality of the South Carolina data categorized by time since last exposure, compared to the fit of the EPA model. Although the 2-stage model fits the data only marginally well ($p = 0.05$), it fits the data much better than the EPA model ($p < 0.001$). The EPA model underpredicts the number of cases for short times since end of exposure.

Table 6-9

Table 6-10

The results with the South Carolina data provide a stark contrast to the Wittenoom results. With the South Carolina data, the model with v dose-related provided the best fit. Thus, the results from South Carolina suggest that chrysotile may be acting primarily as an initiator. Such an interpretation must be tempered, however, by several inconsistencies and potential problems with the South Carolina fits that may be attributed, among other possibilities, to the short half-lives assumed for chrysotile.

The two fits (for South Carolina and Wittenoom) also provide very different estimates of the background parameters (v_0, α_0 and μ_0). The μ_0 and v_0 estimated from the South Carolina data both are about 250 times larger than those estimated from the Wittenoom data. Although these rates could differ somewhat in these cohorts, owing to different lifestyles and genetic traits in the two populations, these differences appear too large to be attributable to such causes.

Due to the apparently conflicting results from the analyses of the lung cancer data from Wittenoom and South Carolina, we conducted several additional analyses to attempt to identify the source of the apparent conflict. We initially explored the possibility that the assumed half-life for crocidolite was too long and completed additional model runs assuming a 0.5 yr half-life (identical to what was assumed for South Carolina) and these results are described below. Subsequently, we discovered during our analysis of time-dependence using the EPA model (see Section 6.2.1.1), that the half-lives measured in vitro for these fibers are likely much too short, which suggests a solution to the apparent conflict and this is also described below. Unfortunately, however, this revelation came too late to allow additional, confirmatory runs with the two-stage model to be completed in time for this report. Therefore, the apparent conflict between the Wittenoom and South Carolina results (at least with regard to the two-stage model) remains to be definitively resolved.

The results of the two-stage model are based on the assumption that one of the two-stage parameters is a linear function of the instantaneous body burden predicted by a first order retention model that relies on dissolution lifetimes for the asbestos fibers that are observed in vitro (Section 7.2.4). Alternately, it could be the case that an inhaled fiber is soon neutralized in some manner (e.g. by some type of sequestration mechanism) so that any contribution to cancer induction must occur soon after exposure. To explore this possibility, the two-stage model was also fit to the Wittenoom data assuming a half-life of only 0.5 year (the same value used for the South Carolina cohort) and results are indicated in Table 6-11.

When the Wittenoom data are evaluated assuming a fiber half-life of 0.5 yrs, as was the case using a 20-year half life, the best-fitting of the three submodels considered was the one with α dose-related. This fit using this submodel was not appreciably worse than that obtained assuming a 20-year half life (difference in likelihoods of 1.16).

Table 6-11

However, with a 0.5-year half-life, the fit of the model that assumed μ was dose-related was appreciably worse than the comparable model assuming a 20-year half life (change in likelihoods of 5). As this analysis demonstrates, choice of an appropriate internal dose can be confounded with selection of the appropriate two-stage parameter that is affected by that dose. The analysis also implies that, due to the number of variables that can be optimized, the two-stage model does not appear to be a good discriminator for evaluating the biodurability of fibers.

These results do not suggest that asbestos acts at short times and is then sequestered. However, they do suggest that favored dose-dependent variables may be strong functions of other constraints placed on the model (such as the assumed half-life of the fibers). This further implies that the South Carolina results reported above might be anomalous, due to the assumption of a half-life that is short relative to the actual rate at which risk is observed to decrease for this cohort (based on the results from the analysis using the EPA model, Section 6.2.1.1).

It is unfortunate that it now appears that we may have evaluated these data using the wrong estimates of dissolution half-lives (which were, nevertheless, based on the best estimates from the literature). Our analysis of the time-dependence of the data using the EPA model (Section 6.2.1.1) suggests that both crocidolite and chyrsotile dissolve in vivo much more slowly than in vitro studies suggest and that this should not be surprising given that such materials only dissolve at their optimum rates when the fluid they are dissolving in is rapidly and continually renewed. Fluid flow rates in most compartments of the lung may simply not be adequate to facilitate dissolution of asbestos at the maximum rate.

It would be interesting to rerun the Moolgavkar model using half-lives based on what was observed with the analyses using the EPA model (approximately 20 years for chrysotile and > 700 yrs or virtually infinite for crocidolite). The goal would be to determine whether the fitting the South Carolina data might then show that chrysotile also acts primarily as a promoter (in agreement both with what is observed for Wittenoom and with what is indicated by the most current mechanism studies, see Sections 7.3.3.4 and 7.3.4.7).

That the two-stage model with v dose-dependent only marginally fits the time-dependence of the South Carolina data, may further reflect the inadequacy of this model (because the assumed half-life for asbestos is much too short). Incorporating a longer half life may improve this fit. In contrast, model fits for Wittenoom in which longer half-lives were assumed (although still short based on observations reported from our analysis using the EPA model), do adequately describe the time-dependence for lung cancer mortality observed in that cohort. As previously indicated, however, the marginal benefit derived from the two-stage model in this application may not be justified compared to the cost and effort that may be required to obtain the new results. Especially given that we can now address questions concerning bio-durability with the adaptation we developed for the EPA lung cancer model (Section 6.2.1.1).

6.2.2 Estimating K_L's from the Published Epidemiology Studies

The EPA model for lung cancer (described in Section 6.2.1.1) was applied to each of the available epidemiology data sets to obtain study-specific estimates for the lung cancer risk coefficient, K_L. Based on the results presented in Section 6.2.1.1, there is no indication that the current model does not provide an adequate description of lung cancer mortality, at least in association with exposure to amphiboles. There is some indication that the current model may not provide an adequate description of the time-dependence of mortality following exposure to chrysotile. However, it is believed that the effect that such deviations might have on estimates of K_L derived using the model are likely to be small, except in rare cases when studies incorporate long periods of followup after cessation of exposure. It will be prudent to evaluate the observed deviations further (if additional raw data sets can be obtained) and to adapt the current model to account for the observed effect, should it be confirmed in other studies. However, at this point in time, we see no reason not to proceed with the analysis of published studies using the existing model.

The set of K_L values derived from available epidemiology studies are presented in Table 6-12. Note that this table is a reproduction of Table A-1 in Appendix A.

In Table 6-12, Column 1 lists the fiber types for the various studies, Column 2 lists the exposure settings (industry type), and Column 3 indicates the specific locations studied. Column 4 presents the best estimate of each K_L value derived for studies, as reported in the original 1986 Health Effects Update and Column 5 presents the reference for each respective study. Columns 6, 7, and 8 present, respectively: the best-estimates for the K_L values derived for all of the studies currently available (including studies corresponding to those in the original Health Effects Update); the estimated lower and upper bounds for each K_L value (derived as described in Appendix A); and the reference for the respective study from which the data were derived. To assure comparability across studies, values for all studies (even those that have not been updated since their inclusion in the 1986 Health Effects Update) were re-derived using the modified procedures described in Appendix A. The remaining columns of the table present information relevant to risk coefficients for mesothelioma and are discussed in Section 6.3.2.

The K_L values derived in this study and the corresponding values derived in the original 1986 Health Effects Update generally agree; most vary be no more than a factor of 2, a couple vary by a factor of 3, and one varies by a factor of about 5. In no case, however, are the differences significant (based on visual comparison of confidence intervals).

Table 6-12

Perhaps the most interesting of the changes between the 1986 K_L value estimates and the current K_L value estimates involves the friction products plant in Connecticut (McDonald et al. 1984). Although a relatively small, positive dose-response was estimated from this study in the 1986 Health Effects Update, the best current estimate is that this is essentially a negative study (no excess risk attributable to asbestos). The difference derives primarily from allowing α to vary in the current analysis. The exposure groups in this cohort do not exhibit a monotonically increasing dose-response relationship and, in fact, the highest response is observed among the group with the lowest overall exposure. Thus, the most likely explanation for the observed relative risk in this cohort is that there is poor agreement in the background cancer rates between the study cohort and the control population. As indicated in Appendix A, lack of a monotonically increasing dose-response relationship is a problem observed in several of the studies evaluated.

Among the K_L values derived in the current study, the lowest and highest of the best-estimate values differ by a factor of 90 (excluding the two negative studies, which would make the spread even larger) and several of the pair-wise comparisons across this spectrum are significant (based on a comparison of their confidence intervals). For example, the K_L value derived for the chrysotile miners in Quebec is significantly smaller than the K_L values derived for chrysotile textile workers (in either of the two studies for South Carolina, which are of highly redundant cohorts in the same plant), for textile workers in the Roachdale, UK plant, and amosite insulation manufacturers (in the Seidman study).

The K_L values and the associated confidence bounds derived in the current study are plotted in Figure 6-3. Each exposure environment is plotted along the X-axis of the figure and is labeled with a four-digit code that indicates fiber type (chrysotile, mixed, crocidolite, or tremolite), industry (mining, friction products, asbestos-cement pipe, textiles, insulation manufacturing, or insulation application); and a two-digit numerical value indicating the study from which the data were derived. A key is also provided. In the Figure, the chrysotile studies are grouped on the left, amphibole studies are grouped on the right, and mixed studies are in the middle. Note also that studies conducted in the same facility (generally among highly overlapping cohorts), such as the Dement et al. (1994) and the McDonald et al. (1983a) studies of the same South Carolina textile facility, are combined (averaged) and presented as a single entry in the Figure. The two Libby Vermiculite studies were similarly combined.

Figure 6-3

Key for Figure 6-3

Comparisons of K_L values across the available studies are instructive. Within chrysotile studies alone, lowest and highest K_L values vary by approximately a factor of 80 (again, excluding the negative friction products study), which is little different than the range observed across all studies. Moreover, as indicated above, the differences between the lowest (non-zero) value (for Quebec miners) and the highest value (textile workers) is significant. Differences between the negative friction product study and the other K_L estimates for chrysotile are not significant, primarily due to the wide confidence interval associated with the negative study.

Among the apparent variations, differences in lung cancer potency observed among Quebec miners versus that observed among South Carolina textile workers has been the subject of much discussion and evaluation, which is worthy of review (Section 6.2.3). In fact, the inability to reconcile these differences, appears to be among the biggest obstacles to reliably estimating an overall chyrsotile potency factor for lung cancer.

Among "pure" amphibole studies, the lowest and highest of the best-estimate K_L values vary by a factor of approximately 20 and, interestingly, the two extremes both derive from within the same industry (amosite insulation). However, these two estimates for amosite insulation are not significantly different (based on a comparison of their confidence intervals) Taking the arithmetic mean of the values for the two amosite insulation studies, results indicate that K_L values estimated, respectively, for crocidolite mining, amosite insulation manufacture, and mining of vermiculite contaminated with tremolite vary by less than a factor of 3, which constitutes stellar agreement (given the magnitude of the associated confidence intervals, as shown in Figure 6-3), if this is indeed the appropriate interpretation. However, alternate interpretations cannot be excluded.

As indicated in Section 6.2.3, for example, it is possible that mining studies tend to exhibit low K_L values relative to studies of asbestos products industries. As indicated in that section, this may be due to the presence of large numbers of cleavage fragments in the dusts, which may not contribute to biological activity (because the majority of these may not exhibit the requisite size to be biologically active) but which, nevertheless, are included in estimates of asbestos concentrations in the original epidemiology studies. Under this interpretation, the K_L estimates for Libby and for Wittenoom might both be raised substantially, if they could be adjusted for similar effects, so that they are closer in value to that obtained from the Seidman study. Then the "outlier" Levin study might be re-evaluated to see if inadequate consideration of lag, the relatively young age of the cohort studied, or other factors might contribute to a low K_L estimate for this study. As indicated in Section 6.2.3, such considerations have implications both for identifying appropriate size ranges of structures to be included in the analysis of asbestos and for evaluating the relative potency of chrysotile and the amphiboles. Of course, because the difference between the K_L values from the Levin et al. study and the Seidman study do not appear significant, such differences may simply be due to unavoidable statistical variation.

It is also instructive to compare variation within and between industries. Within industries (especially for a single fiber type), the data are limited. The studies from the two chrysotile mines (Quebec and Italy) show remarkably close agreement, varying by less than about 20%. However, the studies of the two amosite insulation plants (Paterson, New Jersey and Tyler, Texas) show K_L values that vary by a factor of 20; due primarily to the uncertainty of the K_L value for the Tyler facility; these differences are not significant. As previously mentioned, the same equipment (literally) was used at both of these insulation plants and the sources of asbestos were also apparently similar, although the cohorts at the two plants are entirely independent.

The differences between the K_L values from the New Jersey and Texas facilities may represent the practical limit to agreement within industries that can be expected. However, it is also possible that an "explanation" for the difference may eventually present itself.

Across all asbestos types (including mixed), the asbestos-cement pipe industry shows the greatest variation, including a negative study (best estimate $K_L = 0$) and three positive studies with K_L values that range amongst themselves by a factor of 17. The friction products industry includes one negative and one positive study. Better agreement is observed among textiles. The two mixed textile plants show K_L values that vary by no more than a factor of 2.5 from each other and from the pure chrysotile textile plant value. However, given the variation observed within other industry groups, such agreement may be fortuitous.

K_L estimates within the mining industry (but between fiber types) range over a factor of 20, from a low of 0.029 for Quebec miners to a high of 0.62 for tremolite in vermiculite miners. Based on inspection of confidence intervals, however, none of the pairwise differences within this industry appear significant.

6.2.3 The Variation in K_L's Derived for Chrysotile Miners and Chrysotile Textile Workers

The difference between the observed risk of lung cancer for comparable levels of chrysotile exposure among Quebec miners (most recent followup: Liddell et al. 1997) and South Carolina textile workers (McDonald et al. 1983a and Dement et al. 1994) has been the focus of much attention. Although the discrepancy in lung cancer risk between Connecticut friction products workers (McDonald et al. 1984) and South Carolina textile workers is potentially even greater (Table 6-12), the large uncertainties associated with the risk estimate in the friction products study make comparisons with friction products more difficult to evaluate (Section 6.2.2). Moreover, reasonably good agreement between results from the Quebec studies and another study of chrysotile miners in Italy (Piolatto et al. 1990) coupled with reasonably good agreement between results from the South Carolina Plant and results from two other textile plants: one in Mannheim, Pennsylvania (McDonald et al. 1983b)and one in Roachdale, England (Peto 1980), suggest that the difference between Quebec and South Carolina may reflect a

general difference between the two industries, rather than specific locations (see Table 6-12 and Section 6.2.2). This appears true despite the fact, for example, that cohorts at the two other textile plants may have been exposed to mixed fiber types (amphiboles as well as chrysotile), see Appendix A and Section 6.2.2. Importantly, this "discrepancy" has been recognized as an issue for lung cancer only, the differences in mesothelioma rates observed in the Quebec mines and the South Carolina textile plant are not widely disparate (see Table 6-12).

Three main hypotheses have been advanced to explain the difference in the risk per unit exposure observed among miners and textile workers (see, for example, Sebastien et al. 1989). These are:

(1) the low reliability of exposure estimates in the various studies;

(2) differences in fiber size distributions in the two industries (with textile-related exposures presumably involving greater fractions of longer fibers); or

(3) simultaneous exposure to a co-carcinogen (oil that may have been sprayed on the asbestos fibers) in the textile industry.

It has also been proposed that differences in the concentration of long tremolite (amphibole) fibers in dusts from each of the two industries might represent an explanatory factor (see, for example, McDonald 1998b). However, this would also require a large relative difference between the potencies of tremolite (amphiboles) and chrysotile toward the induction of lung cancer. This latter issue is addressed further in Section 6.2.4. McDonald (1998b) also presents an overview of the current status of each of the hypotheses described above.

In an attempt to distinguish among the above-listed hypotheses, Sebastien et al. (1989) conducted a study to determine lung fiber concentrations in tissue samples from deceased members of the cohorts studied from both the Quebec mines (specifically, from the Thetford mine) and the South Carolina textile plant. These researchers ultimately analyzed tissue samples from 72 members of the South Carolina cohort and 89 members of the Thetford (Quebec) cohort. Because the tissue samples came from cohort members, they could be matched with estimates of the exposure experienced by each of the individuals as well as details concerning the age at first employment, the age at death, the years of employment, and the number of years following employment until death.

In the Sebastien et al. study, tissue samples were obtained in formalin-fixed or paraffin blocks, which were then digested in bleach, filtered, and analyzed by TEM. Tissue samples were apparently "opportunistic." Only fibers longer than 5 µm with an aspect ratio greater than 3:1 were included in the count. For consideration of the limitations associated with such preparations, see Section 5.2.

Results from matching of tissue samples with the histories of corresponding cohort members indicate that tissue samples obtained from each cohort covered a broad range of exposure levels, duration of exposure, and years since the end of exposure. They also indicate that South Carolina cohort members included in the Sebastien et al. study experienced, on average, 13.5 years of exposure with 18.1 years between the end of exposure and death. In contrast, Thetford workers included in this study experienced an average of 32.6 years of exposure with only 11.6 years between the end of exposure and death. Corresponding to differences in exposure levels observed across the two cohorts in the original epidemiology studies, mean exposure levels experienced by Thetford cohort members included in this study were about 10 times mean exposure levels experienced by South Carolina workers (19.5 mpcf vs. 1.9 mpcf).

Because Sebastien and coworkers recognized the general lack of a good model describing the retention and clearance of asbestos fibers in the lungs at the time their study was conducted, they performed most of their analyses either on pairs of members (one from each cohort) matched for duration of exposure and time since end of exposure or on groups of members from each cohort similarly stratified by duration of exposure and time since end of exposure.

Results from their study indicate that, overall, lung burdens observed among Thetford cohort members are substantially higher than those observed among South Carolina cohort members. Geometric mean lung chrysotile concentrations are reported to be 5.3 and 0.63 fibers/µg dry lung tissue in Thetford workers and South Carolina workers, respectively. Furthermore, despite tremolite representing only a minor contaminant in the chrysotile from Quebec and the dusts to which the miners were exposed (Sebastien et al. 1986), the majority of fibers observed in the lungs of Thetford miners were in fact tremolite (mean concentration 18.4 f/µg dry lung). Since the raw material used in the South Carolina plant came largely from Quebec, tremolite was also expected to be a minor contaminant in the dusts to which textile workers were exposed. Yet among these workers also, tremolite represented a substantial fraction of the lung fibers observed (mean concentration 0.36 f/µg). Thus, the ratio of tremolite concentrations observed among Thetford miners and that observed among South Carolina workers (18.4:0.36 or 51) is even more extreme than the ratio observed for chrysotile (8.4).

To evaluate the first of the above-listed hypotheses, it is instructive to compare the ratios of chrysotile or tremolite fibers observed in the lungs of deceased workers from Thetford and South Carolina, respectively, with the overall exposures that each received. A rough estimate of cumulative exposure for each set of workers in the Sebastien et al. (1989) study representing each cohort can be derived as the product of the mean duration of exposure and the mean intensity of exposure. Thus, for example, mean cumulative exposure in Thetford was 32.6 years x 19.5 mpcf or 635.7 mpcf-yrs. Similarly, for South Carolina, mean cumulative exposure was 25.65 mpcf-yrs, which gives a Thetford/South Carolina ratio of 24.8. This presumably represents the relative cumulative exposure to chrysotile. For tremolite, Sebastien et al. report that, based on a regression analysis, air concentrations of tremolite were likely only 0.4 times as much

in South Carolina than in Thetford (where they likely averaged 1% of total fibers). Therefore, the ratio of cumulative exposures to tremolite for the sets of cohort members studied by Sebastien is likely 62.

Comparing the ratio of Thetford:South Carolina lung burden estimates with the ratios of the corresponding cumulative exposures, it appears that the chrysotile lung burden ratio (8.4) is only a third of the ratio predicted based on cumulative exposure (24.8). However, the ratio of lung tremolite concentrations (51) is much closer to the corresponding cumulative exposure ratio (62). It thus appears that, although, airborne concentrations may not closely track the exposures that led to the observed lung burdens, the overall trend in exposures predicted by airborne measurements is approximately correct. It is therefore likely that overall exposure concentrations in Thetford were in fact substantially higher than in South Carolina (in agreement with airborne measurements). Thus, we concur with Sebastien et al. that the unreliability of exposure estimates in these two cohorts is unlikely to explain the observed difference in the risk per unit of exposure observed for each cohort.

Importantly, although the general trend in relative overall exposure levels predicted by airborne measurements between Thetford and South Carolina appear to have been confirmed by mean lung fiber concentrations in the Sebastien et al. (1989) study, estimated exposures appear to do a very poor job of predicting lung burdens for any particular individual. To demonstrate this, we analyzed the Thetford: South Carolina ratios of lung chrysotile concentrations and, separately, lung tremolite concentrations reported by Sebastien et al. for their set of 32 matched pairs of cohort workers to determine whether trends in these ratios adequately matched trends in the corresponding estimated airborne exposure level ratios for the same matched pairs. To do this, we subjected the ratios presented in Table 7 of the Sebastien et al. (1989) study to a Rank Von Neuman test (Gilbert 1987). Results indicate that trends in neither lung chrysotile concentration ratios nor lung tremolite concentration ratios can be predicted by the observed trend in the estimated airborne concentration ratios among these 32 matched pairs.

There are numerous sources of potential uncertainty that may mask the relationship between airborne exposure estimates and resulting lung burdens (Section 5.2). Potentially the largest of these is the variation expected among lung burden estimates derived from use of “opportunistic” tissue samples, which are not controlled for the portion of the respiratory tree represented by the sample. Even for samples collected from adjacent locations in lung parenchyma, observed fiber concentrations may vary substantially and such variation is magnified between samples taken from different individuals at locations in the lung that may not in any way correspond to their relative position in the respiratory tree.

Other potentially important sources of variation that may mask the relationship between airborne exposure concentrations and resulting lung burden estimates may primarily involve limitations in the degree to which the airborne estimates from an epidemiology

study represent actual exposures to the individual members of a study cohort (Section 5.1). Thus, such things as: potential differences between individual exposures versus area concentrations (which are what is typically measured), the adequacy of extrapolation to the earliest exposures in a cohort (when measurements were generally not available), or the adequacy of estimating job x time matrices for individual workers that can then be integrated with work area exposure estimates to derive individual exposure estimates may all contribute to the uncertainty of exposure estimates.

The second of the above-listed hypotheses, involves potential differences in the size of structures that may have been present in the airborne concentrations in Thetford and South Carolina, which may not have been adequately represented by the exposure measurements. More generally, this is a question of the degree to which measured exposures in the two environments adequately reflect potential differences in the character of exposure that relate to biological activity.

Sebastien et al. (1989) considered this second hypothesis by generating and comparing size distributions for the fibers observed in the lungs of workers from Thetford and, separately, South Carolina. Importantly, the size distributions for each cohort were generated by including the first five fibers observed from every member of that cohort, without regard to the duration of exposure, level of exposure, or time since exposure experienced by each cohort member. Therefore, the size distributions obtained are "averaged" over very different time frames during which differing degrees of fiber retention and clearance will have taken place, each of which potentially alters the distributions of fiber sizes (Section 7.2). Thus, the two distributions generated are each actually collections of samples from multiple, varied size distributions (rather than single distributions) and this likely masks distinctions between the two work environments. It is therefore not surprising that the authors found relatively little differences in the two size distributions.

The portion of the generated size distributions that are least likely to have been affected by the limitations due to the manner in which they are generated (as Sebastien et al. suggest) is the fraction of tremolite (amphibole) fibers longer than 20 µm. This is because (1) tremolite fibers (unlike chrysotile) are biodurable and (2) biodurable fibers longer than approximately 20 µm have been shown to clear from the lung only very slowly, if at all (Section 7.2). Thus, the Thetford:South Carolina ratio of long tremolite fibers may provide the best indication of the relative size distributions in the two environments.

Table 6-13 presents a table of the estimated, relative concentrations of specific lengths of fibers observed in lung tissue among Thetford miners and South Carolina workers, respectively. The length category for various fibers is presented in the last column of the table. The estimated concentrations, presented in Columns 2 (for Thetford) and 3 (for South Carolina) of this table were derived as follows. For the first length category (L > 5 µm), concentrations are taken directly from Table 5 of the Sebastien et al. paper (the geometric means are presented). Concentrations for the remaining length

categories were estimated by multiplying the concentrations for this first length category by the fraction of the size distribution represented by each succeeding length category (as provided in Table 4 of the Sebastien et al. paper). So that the relative precision of these concentration estimates can be evaluated, an estimate of the numbers of fibers included in each length category (from the total used to derive the size distribution in Table 4 of Sebastien et al.) are provided in Columns 6 (for Thetford) and 7 (for South Carolina), respectively. The Thetford:South Carolina ratios of the concentrations of fibers in each length category (for each fiber type) are provided in Column 5 of the table.

It is instructive to compare the ratios presented in Table 6-13 to the Thetford:South Carolina ratios of mean cumulative exposures estimated above for chrysotile and tremolite among the cohort members included in the Sebastien et al. study (24.8 and 62, respectively). As indicated in Table 6-13, for chrysotile, the ratio remains approximately constant at about 9 (varying only between 8.4 and 10) for all of the size ranges reported except the longest. For the longest category (L > 20), however, the ratio drops to 5. Because fibers longer than 20 µm are expected to be the most persistent in the body (Section 7.2), it may be that the ratio of 5 best represents the relative concentration of long chrysotile structures among the two sets of cohort members.

Because this ratio (for the long fibers found in the lung) is only approximately one fifth of the estimated ratio for the cumulative exposure to chrysotile (24.8), this suggests that the South Carolina cohort may indeed have been exposed to dusts enriched in long fibers relative to dusts experienced at Thetford. Because the estimate of this ratio is based on counts of at least 11 fibers from Thetford and South Carolina, respectively, it is unlikely that this ratio will vary by more than a factor of two or three (the 95% confidence interval around 11 fibers, based on a Poisson distribution is 6 to 19).

Table 6-13

The trend with tremolite is even more striking. Moreover, as previously indicated, because tremolite fibers are biodurable, it is the tremolite fibers longer than 20 µm that may best represent the ratio of long fibers to which these two groups of cohort members were exposed. The ratios observed among tremolite fibers steadily decrease from approximately 50 for fibers longer than 5 µm to 4.4 for fibers longer than 20 µm, although this last value is uncertain (due to it being based on only 1 fiber observed among Thetford-derived lungs and only 4 fibers among South Carolina-derived lungs). In fact these data are statistically consistent even with a ratio considerably less than one, (i.e., with a considerably higher concentration of long tremolite fibers in South Carolina than in Quebec). Given that the ratio of the original cumulative exposures for tremolite was estimated to be 62, that the ratio of long tremolite fibers is only 4.4 suggests that dusts in South Carolina may have been highly enriched in long fibers.

Observations that the fibers to which textile workers were exposed were longer and thinner than those found in mining are further supported by various published size distributions of fibers determined in air samples collected in these environments (see, for example, Gibbs and Hwang 1975, 1980). Also, as noted in Curmp et al. (1985), the raw fiber purchased by textile plants was commonly described as the longest grade of product (see Table 22 of Crump et al.) Size issues are addressed further in Section 6.2.4.

At this point it is worth mentioning some of the potential differences in the characteristics of mining dusts and textile mill dusts that may affect biological activity, but that may not be adequately delineated when measuring exposures by PCM (in f/ml) and almost certainly not delineated when exposures are measured by midget impinger (in mpcf), see Section 4.3. During the mining of asbestos, only a small fraction of the rock (generally no more than 10%) that is mined is typically composed of the fibers of interest.

While the host rock in a mine may be of similar chemical composition, it generally represents an entirely different crystalline habit. Nevertheless, a large fraction of the dust that is created during mining is likely composed of fragments from the host rock and many of these fragments will be of a size that would be included in the particles counted by midget impinger. Furthermore, at least some fraction of the fragments created by the crushing and cutting of the host rock will be elongated “cleavage” fragments (Section 4.0) so that at least some fraction of these may be included even in PCM counts, despite many of them being either too thick to be respirable or too short or thick to be biologically active (see Section 7.2). Note, although Sebastien et al. employed TEM to characterize fibers in their 1989 study, they apparently employed a fiber definition that was sufficiently broad that they too would have counted large numbers of structures that may not contribute to biological activity.

In comparison, the dusts created in a textile factory are likely composed almost exclusively of true asbestos fibers. The raw material received by the factory will already have been milled and beneficiated to remove the vast majority of non-fibrous material.

It is therefore, much less likely that extraneous fragments (even cleavage fragments) exist that might be counted either by midget impinger or PCM. We make this point because, if this represents the true situation, it would be expected that risk per unit exposure estimates (i.e. dose-response factors) derived from any mining site, may be smaller than estimates derived for the same fiber type in occupational environments where only finished fiber is used. Thus, another interpretation of the variation observed among estimated K_L and K_M values for amphiboles (reported in Section 6.2.2 and Section 6.3.2, respectively) is that the mining values are somewhat low. The implications of this possibility are discussed further in each respective section.

Note, although the Sebastien et al. paper suggests that (mpcf) exposure estimates from Thetford and South Carolina grossly suggest the relative range of lung burdens observed, there is too much scatter in the data to determine how closely the air ratios track the lung burden ratios. For example, ratios derived from arithmetic means (rather than the geometric means) for the Sebastien et al. data are substantially different. Moreover, as indicated above, there may be substantially different size distributions in the two environments, which might at least in part be explained by the inclusion of large numbers of cleavage fragments (with dimensions inappropriate for biological activity) in the mining environment.

Although the third of the above-listed hypotheses was not addressed by Sebastien and coworkers, the question of whether a co-carcinogen contributes to the overall observed lung cancer rate among textile workers has been considered by several other researchers. To test the hypothesis of whether oils potentially contributed to disease in South Carolina, Dement and Brown (1994) performed a nested case-control study among a subset of the cohort members previously studied by Dement et al. (most recent update, 1994). In this analysis, Dement and Brown qualitatively assessed the probability of mineral oil exposure for cases and controls based on knowledge of historic descriptions of mineral oil use. The extent of such exposure was then further categorized into three strata: none or little, moderate, or heavy, based on where each worker was longest employed. Cases and controls were then further categorized based on years at risk and level of asbestos exposure. Results from this nested analysis indicated no significant change in the estimated exposure-response slope for asbestos after adjusting for mineral oil exposure.

Additional, albeit qualitative, evidence that oils may not represent an adequate explanation for the relative lung cancer risks observed in mining and textiles is provided by McDonald (1998b). McDonald suggests that oils were not used in the Roachdale plant until 1974. Therefore, due to latency, it is unlikely that the use of such oils would have had a substantial impact on the observed lung cancer cases at the point in time that the study was conducted (Peto 1980).

Taken as a whole, the evidence presented in this Section suggests that the relative distribution of fiber sizes found in dusts in the textile industry and the mining industry,

respectively, may be the leading hypothesis for explaining the observed differences in lung cancer risk per unit of exposure between these two industries.

6.2.4 Evaluating Effects Associated with the Character of Exposure

As indicated in Chapter 3(Overview), valid extrapolation of risk coefficients derived from a reference site for use at a new site (to predict risk) requires that both of the following two conditions be satisfied:

(1) that asbestos be measured in both environments in an identical manner; and

(2) that such measurements reflect (or at least remain proportional to) the characteristics of asbestos exposure that determine biological activity.

Because there is mounting evidence that the manner in which asbestos was measured in the available epidemiology studies may not adequately reflect the characteristics that relate to biological activity (Section 7.4 and 7.5), the second of the above two criteria may not be satisfied when dose-response factors (i.e. K_L's and K_M's) derived from these studies are used to predict risk in new environments, without first applying some type of adjustment. Therefore, we explored the possibility that an improved index of exposure could be identified and that dose-response factors from the available human epidemiology studies could be adjusted so that they could be matched with measurements based on an improved exposure index to predict risk.

Based on an extensive evaluation of the broader literature and the results from a series of supplemental studies (Chapter 7), the primary features required of an improved index of exposure were identified and an "optimum" exposure index was defined. As indicated below, however, compromises were required to adapt the risk coefficients derived from human epidemiology studies to match measurements using the improved index. Due to the limitations of the data available for adjusting the existing K_L's and K_M's, an improved, but less than optimum exposure index was defined, which nevertheless represents the best of adjustments that can be justified, based on existing data.

Following a description of the procedures employed to adjust the existing K_L's and K_M's, the effects of such adjustments and their appurtenant implications for risk assessment are explored.

6.2.4.1 Adjusting K_L's for size

As previously indicated, considerations necessary to compare risk coefficients derived in different exposure settings (or to apply a coefficient to predict risk in a setting different from the one in which the coefficient was derived) have been elucidated clearly in a mathematical model (Chesson et al 1989). The consequences of the model

indicate that adjusting the existing risk coefficients so that they reflect asbestos characteristics that determine biological activity requires knowledge of the fiber size distributions of the dusts studied in the *original* epidemiology studies. To the extent they exist, such data may be used to normalize each of the published risk coefficients so that they relate to a common exposure index reflecting asbestos characteristics that determine biological activity.

Adjustment of the existing risk coefficients is necessary because they have all been derived based primarily on PCM and MI measurements and neither PCM nor MI measurements relate adequately to biological activity (Section 7.5). Thus, analytical techniques employed at the time these studies were conducted were not capable of providing asbestos measurements that directly reflect biological activity.

Ideally, the existing risk coefficients should be adjusted so that they are all normalized to an exposure index such as that defined by Equation 7.12, which has been shown to adequately reflect the characteristics of asbestos that determine biological activity (Section 7.5). However, as indicated below, the database available for describing structure-size distributions for exposures in the original epidemiology studies do not contain sufficient information to individually characterize frequencies for structures in separate length categories longer than approximately 10 µm, while Equation 7.12 requires that fibers longer than 40 µm be separately enumerated. Therefore, an ad hoc exposure index is presented, which represents a compromise between theoretical needs defined in Chapter 7 (Section 7.5) and the limitations of the available data.

Importantly, the conclusions that can be drawn from a review of the general asbestos literature (Section 7.5) is that the asbestos fibers that drive risk are almost certainly longer than 10 µm with potency likely increasing for longer structures, at least up to a length of 20 µm. Therefore, due to the fact that structures longer than 20 µm have not been adequately characterized in any of the epidemiologically studied environments, it is not possible to test optimal exposure indices such as the one defined in the earlier analysis of animal inhalation studies (Berman et al. 1995). At the same time, it is apparent that an exposure index focusing on structures longer than 10 µm as the primary contributors to risk should be superior to the arbitrary index originally defined for PCM analysis and employed in the original epidemiology studies. Moreover, the new index proposed here is also limited to structures that are clearly respirable and includes counting of even the thinnest of respirable structures while the index defined for PCM does neither (Appendix B).

In the remainder of this section, the K_L's derived in Section 6.2.2 (and summarized in Table 6-12) are normalized (using a series of published size distributions derived from TEM measurements) to an exposure index that is expected to better reflect biological activity. The distributions are defined for exposure settings that correspond to several of the settings evaluated in the epidemiology studies from which the published risk coefficients were derived. The coefficients are then combined with the asbestos risk models presented previously (U.S. EPA 1986) and evaluated above (Section 6.2.1) to

derive a set of adjusted K_L values (K_{L*}'s), which are appropriately matched for use with the proposed, new exposure index. The proposed, new index is also defined below.

For the lung cancer model and the associated risk coefficient, "K_L," to be applicable generally, the asbestos concentration, "f," needs to be expressed in an exposure index that incorporates the characteristics of asbestos that determine risk. Correspondingly, the risk coefficient, "K_L" needs to be normalized to a model in which "f" is properly expressed.

As indicated previously, published structure size distributions derived from TEM measurements are used to adjust the existing K_L's by normalizing them to an exposure index that is expected to better relate to biological activity than the measurements in the epidemiology studies from which the K_L's were obtained.

Assuming that the available TEM size distributions are representative of dust characteristics for the exposure settings (industries) studied, these were paired with corresponding epidemiology studies. The TEM size distributions are then used to convert the exposure measurements used in the epidemiology studies to the new exposure index that is potentially more characteristic of biological activity. Studies were paired as indicated in Table 6-14

Only a subset of the TEM size distributions listed in Table 6-14 were actually employed in the effort to normalize K_L values. To minimize uncertainty introduced by between-study variability, it was decided to employ distributions from common studies, to the extent that this could be accomplished without reducing the number of "size-distribution -- K_L" pairs available for inclusion in the analysis. Also, studies containing the best documented procedures were favored over those in which the limitations of the distributions were less clear. Ultimately, the size distributions selected for use (with one exception) came from only two studies, which were reported in three publications: Dement and Harris (1979), Gibbs and Hwang (1980), and Hwang and Gibbs (1981). In the case of the one exception, size distributions for Libby (tremolite asbestos in vermiculite) were derived from TEM data recently acquired directly from the site.

Table 6-14

Table 6-15 presents bivariate fiber size distributions derived from the published TEM data that are paired with representative K_L values from the corresponding epidemiology studies. These data were used to adjust K_L values in the manner described below.

The procedure for adjusting risk coefficients is straightforward. First, Equation 6.2 is re-written to reflect the fact that the fiber concentrations, "f," in the original epidemiology studies were typically measured by PCM:

$$K_L(C_{PCM})(d') = RR - 1 \qquad 6.3$$

where:

"C_{PCM}" is the concentration of asbestos structures that are typically included in a PCM measurement (Section 4.3); and

all other parameters have been previously defined.

The left side of Equation 6.3 is then multiplied by one (expressed as a product of reciprocal ratios):

$$\left[K_L\left(\frac{f_{PCME} * C_{tot}}{f_{Opt} * C_{tot}}\right)\right]\left(\frac{f_{Opt} * C_{tot}}{f_{PCME} * C_{tot}}\right)(C_{PCM})(d') = RR - 1 \qquad 6.4$$

where:

"f_{PCME}" is the fraction of asbestos structures in the published size distribution that are typically included in PCM measurements;

"f_{opt}" is the fraction of asbestos structures in the published size distribution that represent the optimal exposure index (i.e. the index of exposure that determines biological activity); and

"C_{tot}" is the concentration of total structures from which the fractions derive.

Remembering that the product of any fraction and the total concentration of a distribution is equal to the concentration of that fraction and that C_{PCME} is supposed to equal C_{PCM} (Section 4.3) and canceling terms accordingly, one is left with a new equation for risk in which asbestos concentrations are expressed in terms of the optimal exposure index:

$$K_{L*}(C_{Opt})(d') = RR - 1 \qquad 6.5$$

where:

"K_{L*}" is now the adjusted risk coefficient, defined (and derived) as described in Equation 6.6:

$$K_{L*} = K_L\left(\frac{C_{PCME}}{C_{Opt}}\right) \qquad 6.6$$

where all terms have been previously defined.

The adjusted risk coefficients, the "K_{L*}s", derived from the data provided in Table 6-15 in the manner described above are presented in Table 6-16. Adjusted risk coefficients for mesothelioma, "K_{M*}'s", are also provided. K_{M*}'s and K_{L*}'s are derived in precisely the same manner. The model adopted for mesothelioma risk is described in the next section.

Ideally, C_{opt} would be set equal to the concentration of asbestos structures defined as described in Equation 7.12. However, as previously described, published size distributions cannot be used to adjust risk coefficients to be consistent with the exposure index described by Equation 7.12. This is because the longest size category individually represented in the published distributions is for all structures longer than 10 µm and the exposure index described by Equation 7.12 requires that structures longer than 40 µm be individually enumerated. Therefore, Equation 7.12 was modified in an ad hoc fashion to generate the exposure index that is evaluated in this document:

$$\mathbf{C_{asb} = 0.003C_S + 0.997C_L} \qquad 6.7$$

where:

"C_{asb}" is the concentration of asbestos to be used to estimate risk;

"C_S" is the concentration of asbestos structures between 5 and 10 µm in length that are also thinner than 0.5 µm; and

"C_L" is the concentration of asbestos structures longer than 10 µm that are also thinner than 0.5 µm.

Although not optimized, as previously indicated, this index is nevertheless expected to represent a substantial improvement over the PCM-related index in current use, because it reflects more of the general criteria for biological activity defined in Section 7.5.

Table 6-15

Table 6-16

The justification for selecting the above exposure index and the potential limitations associated with its use are described in Appendix B. Until such time that a study is completed in which size distributions are generated that allows use of an exposure index incorporating consideration of longer structures (such as that defined by Equation 7.12), it is recommended that asbestos concentrations be defined in terms of the exposure index defined by Equation 6.7 when evaluating asbestos risks. We therefore recommend that this index be incorporated into an interim protocol for conducting asbestos risk assessments.

6.2.4.2 Evaluating the implications of adjusting K_L's for size

To compare the effects of adjusting K_L values for fiber size, the adjusted values (the K_L's), are plotted (along with their associated confidence intervals) in Figure 6-4, which exhibits a format identical to that of Figure 6-3, to facilitate direct comparison. The "key" provided in Figure 6-3 is also directly transferable to Figure 6-4.

At first glance, the two figures look quite similar. However, closer inspection indicates that: (1) two of the points plotted in Figure 6-3 (for MP11 and MX13) are missing in Figure 6-4; (2) the confidence intervals are larger in Figure 6-4 than in Figure 6-3; and (3) the relative location of the best estimate values (central points within each confidence interval) have changed slightly relative to one another. The implications of these observations are discussed below.

Regarding Figure 6-4, the two points missing (for MP11 and MX13) were omitted because it was felt that none of the available size distributions used for adjusting the K_L values were suitably applicable for these study sites, so no conversions were possible. The confidence intervals are larger in Figure 6-4 because, as previously indicated, we have attempted throughout our analysis of the epidemiology data to account for major sources of uncertainty. Thus, the confidence intervals depicted in Figure 6-4 are modified from those depicted in Figure 6-3 to account for the uncertainty of making the adjustment for fiber size using paired data from published size distributions. The intervals were adjusted by multiplying the upper bound and dividing the lower bound by a factor thought to represent the relative contribution to uncertainty contributed by the need to match data from separate studies to perform the conversions. The factors employed are provided in Table 6-17.

The visual impressions from a comparison between Figures 6-3 and 6-4 regarding changes in the relative locations of the central values (best estimate) K_L and adjusted K_L values are subtle. Thus, numerical representations are provided in Table 6-18.

Figure 6-4

Table 6-17

Table 6-18

Table 6-18 presents the magnitude of the spread in the range of original and adjusted K_L values (and also original and adjusted K_M values) estimated as the quotient of the maximum and minimum values of each range. Note that, of necessity, such an analysis requires that the zero values obtained for the Connecticut friction products plant (CF4) be omitted. Note further that the data sets evaluated in Table 6-18 for the original and adjusted values are identical (i.e., the two studies for which no suitable conversion factor could be found were excluded).

In Table 6-18, it is apparent that the spread in values among "pure" fiber types (i.e. chrysotile only or amphibole only) are both smaller than those for mixed data sets (containing both fiber types). This suggests that there may be differences in the potencies of each fiber type toward each respective disease (lung cancer and mesothelioma). In fact, the effect appears to be even more extreme among mesothelioma values than among lung cancer values (discussed further in Section 6.3.3.2). Moreover, that the spread in adjusted values for the data sets containing only the pure fiber types are smaller than for the unadjusted values, but (at least for lung cancer) larger than the unadjusted values for mixed data sets suggests that the effects from adjusting the K_L (and K_M) values for fiber size may be confounded with differences in the potency of fiber types. Therefore, we endeavored to develop a procedure for evaluating these data that would simultaneously account for both fiber size and type.

To address these issues, we considered that the mixed exposure environments represent situations in which there would be combined contributions to risk from both amphiboles and chrysotile. It is also known that chrysotile from the Quebec mines contains small amounts of tremolite (amphibole) asbestos (Sebastien et al. 1986). We therefore set up the following formalism to separate the effects of chrysotile asbestos from the effects of the amphiboles. Note, based on results of a previous study (Berman et al. 1995) and lack of compelling evidence elsewhere in the literature (assuming that size effects are adequately addressed, see Chapter 7), we assume in this formalism that all similarly-sized amphibole fibers are equipotent.

We start by defining potency factors for truly pure fiber types: K_{La} for pure amphiboles and K_{lc} for pure chrysotile. Next we define the relative potency of chrysotile, "RPC" as the ratio of these factors. Thus:

$$\mathbf{K_{Lc} = RPC * K_{La}} \qquad 6.8$$

If one then knows the fraction of amphibole asbestos, f_{amph} in an exposure setting, the relationship between the observed, overall potency factors (e.g. the K_L's) and these fiber-specific factors is given by:

$$\mathbf{K_L = K_{La} * f_{amph} + RPC * K_{La} * (1 - f_{amph})} \qquad 6.9$$

Note that, if RPC = 1 then Equation 6.9 reduces to the identity $K_L = K_{La}$ and Equation 6.8 reduces to $K_{Lc} = K_{La}$, meaning that all fibers are equipotent and there is no distinction for fiber type. Also, if RPC = 0, then chrysotile is non-potent and Equation 6.9 reduces to $K_L = K_{La} * f_{amph}$. Moreover, because f_{amph} is always less than one, this latter equation means that the true potency of the amphibole fibers is greater than would be indicated by the overall K_L in a study (whenever RPC = 0).

Finally, solving Equation 6.9 for K_{La} yields:

$$K_{La} = \frac{K_L}{[f_{amph} + RPC * (1 - f_{amph})]} \qquad 6.10$$

and we further define the denominator on the right side of Equation 6.10 as the function "Q".

Because the value for K_{La} should be constant across all study environments, if we also know the fraction of exposure in each environment contributed by amphiboles, we can apply Equation 6.10 to each of the available K_L's and search for the value of RPC that minimizes the spread in the resulting K_{La} values. Furthermore, by applying this same procedure both to the original K_L values and to the size adjusted K_L values (the K_{L*}'s) allows simultaneous consideration of fiber size and type. Results of applying this analysis are presented in Table 6-19.

The results provided in Table 6-19 are based on the estimates of the fraction of exposures in each environment that is represented by amphiboles presented in Table 6-20. In Table 6-20, the best estimate of the fraction of amphiboles is provided in Column 3 along with an estimate of the range (in Column 4), which indicates the degree of uncertainty that should be associated with each estimate of the fraction of amphiboles. The source of information from which each estimate was derived is provided in Column 5. Note that, depending on the particular study environment, such fractions either represent a time/operations average (e.g. commercial amphiboles were employed in a certain fraction of the plant for a certain period of time) or a composition average (e.g. tremolite constitutes some defined fraction of the chrysotile used).

Table 6-19

Table 6-20

In Table 6-19, the different data sets evaluated (i.e. the K_{La}'s, K_{La^*}*s. K_{Ma}'s, and K_{Ma^*}*s) are identified in Column 1. The number of studies included in each data set is listed in Column 2. Column 3 presents the values of the optimized RPC's (the RPC's for which the spread in K_{xa} values across each data set is smallest). Column 4 presents the minimized (optimum) range in the corresponding K_{xa} values for each data set (expressed as the ratio of the maximum/minimum values). Column 5 presents the corresponding ratio of the original and adjusted K_{xa} values. Column 6 presents this same ratio of original and adjusted K_{xa} values with RPC held fixed at one, and Column 7 indicates which study environments represent the maximum and minimum values for the optimized range of each data set.

Several conclusions can be drawn from the data presented in Table 6-19. First, it appears that, for both lung cancer and mesothelioma, the best estimate is that there is a difference in potency between chrysotile and amphiboles. For lung cancer, chrysotile may only be one third to one half as potent as the amphiboles, depending on whether one also adjusts risk factors for fiber size. For mesothelioma, no matter whether risk factors are adjusted for fiber size or not, it appears that chrysotile is much less potent than amphiboles and, in fact, may be non-potent. However, because improvement in the reconciliation of potency estimates across studies becomes marginal for RPC's smaller than about 1/1000 (and changes are no longer noticeable for RPC's smaller than about 1/10,000), a conservative estimate suggests that, at most, chrysotile is no more than about 1/1000 as potent as amphiboles toward the induction of mesothelioma. Other inferences concerning mesothelioma are addressed further in Section 6.3.3.2.

Although the improvements in reconciliation across potency estimates for the different studies are modest when one adjusts for fiber size (the ranges are decreased by about 30%), these reductions are based on spreads over the entire, available data sets (15 studies for lung cancer and 10 studies for mesothelioma). Moreover, such reductions are achieved using the relatively crude procedure of matching published size distributions to published epidemiology studies (rather than by obtaining true study-specific size distributions). Thus, combined with the strong inferences from the rest of the literature (see Chapter 7) that such size adjustments better reflect the characteristics of biological activity, adjusting values for fiber size is well justified and will improve the confidence with which risks can be extrapolated to new sites.

In this analysis, the range in lung cancer potency estimates is reduced from about a factor of 90 (when data are neither adjusted for fiber size or type, Table 6-18) to 59 (when data are adjusted for both fiber size and type). Interestingly, the extremes of this range are contributed by South Carolina textiles (CT6 - the maximum value) and Quebec mining (CM1 - the minimum value). Once adjusted for fiber size and type, the lung cancer potency estimates from all other studies (including those both for mixed exposures and for nominally pure amphibole exposures) falls between these two extremes. As previously indicated (Section 6.2.3) the differences in potency estimates in these two environments has been the focus of much attention. Based on the

analysis presented in Section 6.2.3, the best of candidate explanations for the differences between mining and textile production is the range of sizes of fibers in these two environments. Further evidence that this is the case is apparent from Table 6-19. As indicated from a comparison of the range in K_L and K_{L*} values in the table, adjusting values for fiber size (even given the crude approach currently available for making such adjustments) already reduces the difference in the potency estimates from these two environments by about 30%.

Although useful, the above analysis of ranges is potentially limited by the need to exclude the nominally zero value from the Connecticut friction products plant (CF4) and the lack of formal consideration of uncertainty. Therefore, an additional analysis was conducted in which uncertainty is addressed formally and the value from the Connecticut study was included.

In this analysis, we assumed that the log of the measured K_L values (or K_{L*}, K_M, K_{M*} values) were normally distributed with mean $Ln\{K_{La}*[f_{amph} + rpc*(1-f_{amph})\}$, where K_{La}, RPC, and f_{amph} were all as previously defined. The variance of K_L was assumed to be composed of two or three independent components. The first component, σ_i, was assumed to be equal to one-half of the difference between the log transforms of the upper limit of the confidence interval and the point estimate of K_L (see Table 6-12). This variance was assumed to represent statistical uncertainty in response and exposure measurements (i.e, uncertainty that the confidence intervals were designed to represent, see Appendix A). Note that these values represent the irreducible fraction of uncertainty in the potency estimates.

A second component, σ, of the standard deviation was assumed to be constant for all studies, and may be thought of as representing the uncertainty in the estimate resulting from differences in exposure conditions, such as fiber size distributions, which are not represented in the σ_i. The overall standard deviation of the K_L from study i was assumed to be $(\sigma_i^2 + \sigma^2)^{½}$. As an alternate approach, the uncertainty in f_{amphi} was incorporated by adding a third independent component of exposure, σ_{ai}, given by one-half of the difference between the log transforms of the upper limit of the confidence interval for f_{amphi} and the best estimate of f_{amphi} (see Table 6-20). Thus, when the uncertainty in f_{amph} was accounted for, the overall standard deviation of the K_L from study i was $(\sigma_i^2 + \sigma^2 + \sigma_{ai}^2)^{½}$.

Using this model, a likelihood test was applied to estimate the parameters, Ln (K_{La}), RPC, and σ, and to conduct likelihood tests of the hypotheses that chrysotile was non-potent (RPC=0) or equally potent (RPC = 1) with amphibole. The same test was applied to the K_{L*}, K_M, and K_{M*} values. When applied to the adjusted (starred) variables, the uncertainty in the fiber size distribution data was not accounted for so that the relative effect of adjusting for fiber size could be evaluated.

In this approach, the overall likelihood is estimated as the product of a series of terms that each represent the likelihood of obtaining a K_L value equal to that obtained from

one of each of the available studies, given that they are derived from a common normal distribution with mean, K_{La} and standard deviation $(\sigma_i^2 + \sigma^2)^{½}$, as indicated above. The optimized (best estimate values) for K_{La} and σ are those for which the overall likelihood is maximized. Results from the analysis with the two parameter standard deviation are summarized in Table 6-21.

In Table 6-21, the first and fifth columns identify the specific data set being considered and the size of each data set is also presented. Columns 2 and 6 indicate the specific variables estimated. Columns 3 and 7 indicate the values for the estimated parameters with the value for RPC optimized. Columns 4 and 8 indicate the values for the estimated parameters with the value for RPC fixed at 1 and Columns 5 and 9 indicate the values for the estimated parameters with the values for RPC fixed at 0.

The results presented in Table 6-21 closely parallel the results obtained from the analysis of the range of values presented in Table 6-19. The best estimated value of relative potency for lung cancer indicates that chrysotile is only between a fifth and a half as potent as the amphiboles toward the induction of lung cancer, depending on whether potency factors are adjusted for fiber size. The results of a hypothesis test indicate that this is not significantly different from the hypothesis that chrysotile and amphiboles are equipotent (in either the original or the size-adjusted data sets). However, the hypothesis that chrysotile is non-potent toward the induction of lung cancer is clearly rejected. Size-adjusting the potency values provides a small improvement (reduction) in the overall variance of the data set of about 3% (although substantially larger improvements are noted for mesothelioma). Assuming the optimal difference in potency for the different fiber types, best estimate K_L and K_{L*} values for chrysotile and amphiboles are also presented in Rows 8 and 9, respectively, of the table. Although the data are not shown, the analysis using the three parameter estimate of standard deviation gave entirely comparable results.

Discussion of the results from the analysis of the mesothelioma values (also presented in the table) is provided in Section 6.3.3.2. Based on this analysis and the rest of the evaluation described in this chapter, a recommended set of lung cancer (and mesothelioma) potency factors has been developed and is presented in Section 6.4.

Table 6-21

6.3 MESOTHELIOMA

The EPA model used to describe the incidence of mesothelioma in relation to asbestos exposure is the model proposed in the Airborne Health Assessment Update (U.S. EPA 1986). This model assumes that the incidence of asbestos induced mesothelioma is independent of age at first exposure and increases according to a power of time from onset of exposure, as described in the following relationship:

$$I_M = K_M \cdot f \cdot [(T-10)^3 - (T-10-d)^3] \quad \text{for } T > 10+d \quad \textbf{(6.11)}$$

$$= K_M \cdot f \cdot (T-10)^3 \quad \text{for } 10+d > T > 10$$

$$= 0 \quad \text{for } 10 > T$$

where:

"I_M" is the mesothelioma mortality observed at "T" years from onset of exposure to asbestos for duration "d" and concentration "f";

"K_M" is the proportionality constant between dose and mesothelioma response and represents the potency of asbestos; and

all other factors have been previously defined.

This is an absolute risk model, which means that the incidence of mesothelioma predicted by the model is a direct function of asbestos exposure that does not depend on the background incidence of the disease. Background mesothelioma cases are rare in the general population in any case.

The EPA model for mesothelioma is the solution to the following integral equation, assuming that exposure remains constant:

$$I_M = 3K_M \int_0^t C(x)(t - 10 - x)^2 dx \quad \textbf{(6-12)}$$

This expression is more general than Equation 6.11, as it applies to both constant and variable exposures (see Appendix A).

6.3.1 The Adequacy of the Current EPA Model for Mesothelioma

Access to the raw epidemiology data from a small number of key studies allowed us to evaluate the adequacy of the EPA model for describing the time-dependence for mesothelioma in asbestos exposed cohorts. For this analysis, the raw data for the cohorts for the chrysotile miners in Quebec was graciously provided by Drs. Liddell and McDonald (described in Liddell et al. 1997), the raw data for the cohort of crocidolite miners in Whittenoom, Australia was graciously provided by Nick DeKlerk (unpublished) and the raw data for the cohort of chrysotile textile workers (described by Dement et al. 1994) was graciously provided by Terri Schnorr of NIOSH. The Whittenoom cohort was originally described by Armstrong et al. (1988), but the data provided by DeKlerk included additional followup through 1999.

To identify potential effects due to varying procedures, different methods for fitting the EPA mesothelioma model to epidemiological data were evaluated. In this evaluation, three methods were used to fit the EPA mesothelioma model to data from Wittenoom.

In the first approach the data were categorized in a manner often available in published form, so this method mimics the method generally used when raw data are not available. The observed mesotheliomas and person years of observation were categorized by time since first exposure, and the mean exposure level and duration of exposure were calculated for each such category. The EPA model is then applied to such data using the approach for the typical situation (as described in Appendix A) and results for the Wittenoom cohort are presented in Table 6-22. The K_M value estimated for Wittenoom using this approach is 7.15E-8 (90% CI: 6.27, 8.11). The fit of this model to data categorized by time since first exposure is good ($p = 0.65$).

Note that, for most of the published epidemiology data sets, the average level and duration of exposure are not available so that these have to be estimated from cruder data, such as cohort-wide averages.

A second approach to fitting the EPA model to epidemiology data, exploits the fact that the mesothelioma model (Equation 6-12) expresses the mesothelioma mortality rate as the product of K_M and an integral involving the exposure pattern, the time of observation, and the ten-year time lag, but not any variable parameters. The value of this integral was calculated for each year of followup of each subject. Person-years of followup and mesothelioma deaths were then categorized according to the values of the integral, and the average value of the integral determined for each category. Results are presented in Table 6-23.

Table 6-22

Table 6-23

K_M was estimated by maximum likelihood from Table 6-23 assuming that the observed numbers of cancer deaths were independently Poisson distributed with a mean equal to the mean value of the integral for that category times K_M. The value of K_M obtained in this fashion was K_M = 9.00E-8 (90% CI: 7.89, 10.2). The fit of the model to data categorized by the integral is not good ($P < 0.00001$), as the model predicts too few mesotheliomas for small values of the integral and too many mesotheliomas for large values of the integral. However, the estimates for K_M obtained from applying the model in this manner are still very similar to those obtained using the exact method (described below).

A third method of estimating K_M (termed the "exact method") employs a likelihood that does not involve any categorization of data. With this method, the hazard function, $h(t) = I_M(t)$ and the corresponding survival function (probability of surviving to age t without death from mesothelioma in the absence of competing causes of death), $S(t) = \exp(-\int_0^t h(s)ds$, are computed for time at the end of followup. The contribution to the likelihood of a subject who died of mesothelioma t_1 years after beginning of followup is $h(t_1)*S(t_1)$, and the contribution of a subject whose followup was not terminated by death from mesothelioma is $S(t_1)$. The complete likelihood is the product of such terms over all members of the cohort. The estimate of K_M obtained by maximizing the logarithm of this likelihood was 7.95E-8 (90% CI: 7.0, 9.0).

We consider the exact method of computing K_M to be the most accurate and results from this method are reported in the summary tables (see, for example, Table 6-12). The Quebec and South Carolina data sets were thus evaluated using the exact method. However, it is noteworthy that the two other methods described above, one of which is often applied to published data, give similar estimates of K_M, at least for this data set.

The Quebec cohort was subdivided into three subcohorts, believed to correspond to differing amounts of amphibole exposure due to tremolite contamination within the chrysotile (Liddell et al. 1997). Location I consisted of workers at the mine at Asbestos where the ore reportedly had less tremolite contamination. Locations 3 and 4 consisted of workers at the large central mine and at smaller mines, respectively, near Thedford, where the ore was more heavily contaminated with tremolite. Location 2 consisted of workers at an asbestos products factory at Asbestos, which processed some commercial amphibole fibers in addition to chrysotile. The exact method of calculating K_M produced the following estimates: Location 1 (8 cases): K_M = 1.3E-10 (90% CI: 0.3E-10, 4.9E-10); Location 2 (5 cases): 9.2E-10, (90% CI: 2.0E-10, 35E-10); Locations 3 and 4 (22 cases): K_M = 2.1E-10 (95% CI: 0.65E-10, 6.5E-10. The relative magnitudes of these estimates track with the relative amounts of amphibole exposure estimated for these locations (Liddell et al. 1997), which is consistent with the hypothesis that the mesothelioma risk in this cohort is due, at least in large measure, to exposure to amphiboles.

There were only two confirmed mesothelioma deaths in the South Carolina cohort and four additional suspected deaths. These were too few to permit detailed analysis.

Based on both confirmed and suspected mesothelioma deaths, the exact method of analysis gave an estimate for K_M of $K_M = 0.43 \times 10^{-8}$, 90% CI: ($0.20 \times 10^{-8}$, 0.79×10^{-8}). Using only the two confirmed mesotheliomas, the same analysis yielded $K_M = 0.14 \times 10^{-8}$, 90% CI: ($0.034 \times 10^{-8}$, 0.38×10^{-8}). The same estimates were obtained by estimating K_M from data categorized by time since first exposure and fitting a linear model to the categorized value of the integral in the definition of the EPA model. Thus, for this cohort (in parallel with the cohort from Wittenoom) comparable K_M values are estimated no matter which of the three methods described above are used for fitting the EPA mesothelioma model to the epidemiology data.

6.3.1.1 Time dependence

The EPA mesothelioma model was next evaluated to determine whether it adequately describes the time-dependence of mesothelioma mortality following cessation of exposure in the Wittenoom and Quebec cohorts. The small number of mesotheliomas observed among the South Carolina cohort precluded our completing this analysis for that cohort. The model predicts that risk rises as the difference between the third power of time since the start of exposure and the third power of time since the cessation of exposure (both lagged by 10 years).

Table 6-24 shows the fit of the EPA mesothelioma model to Wittenoom data characterized by time since last exposure, based on the K_M estimated from the exact analysis. Although this fit appears adequate (P = 0.21), there appears to be a slight tendency for the EPA model to under-predict the mesothelioma rate at long times following cessation of exposure. However, given that the EPA model does not appear to under-predict the mesothelioma rate at long times for the other two cohorts evaluated (see below), it is not clear that this is a real limitation in the model. At the same time, the number of mesotheliomas in the other two cohorts are relatively small. Moreover, both of these other cohorts nominally involve chrysotile exposure (as opposed to crocidolite). Therefore, it may prove useful to obtain additional cohorts (preferably with relatively large numbers of mesotheliomas and preferably involving amphibole exposure) before concluding definitively whether the current EPA mesothelioma model adequately describes the time dependence for mesothelioma.

Table 6-25 shows the observed and expected mesotheliomas in the three separate locations at Quebec, categorized by time since last exposure, and computed using the K_M values obtained using the exact fitting method. Although the small numbers of mesotheliomas make it difficult to draw definite conclusions about the adequacy of the model, there is little evidence that the model under or over-predicts the numbers of mesotheliomas at long periods after the end of exposure.

Table 6-24

Table 6-25

Table 6-26 similarly shows the fit of the EPA model to the South Carolina mesothelioma data (including all four suspected mesotheliomas as real). As with the Quebec cohort, there is little evidence from this cohort that the model under or over-predicts the number of mesotheliomas at long times following the end of exposure. Particularly with this cohort, however, conclusions must be drawn with caution due to the very small number of mesotheliomas observed.

Based on the analysis performed, we see marginal evidence that the current EPA model for mesothelioma may not provide an adequate description of the long term risk of mesothelioma in cohorts exposed to asbestos (even for extended periods of time following cessation of exposure); the fit of the model to the Wittenoom cohort is adequate, despite the small apparent discrepancy at long times. There also appears to be little evidence that there is a difference in the time development of mesothelioma between the Wittenoom and Quebec cohorts, although it is acknowledged that the data from the Quebec cohorts were divided into sets containing only small numbers of mesotheliomas. This latter observation contrasts with what was observed for the lung cancer model, where there is evidence that the effect that chrysotile has on relative risk appears to decrease with time following cessation of exposure while the effects of crocidolite appear to remain constant (Section 6.2.1.1).

If the observed difference in the time dependence for *lung cancer* risk observed for chrysotile (among South Carolina textile workers and Quebec miners) and crocidolite (among Wittenoom miners) is indeed due to fiber type, that a similar effect is not observed for mesothelioma suggests, among other possibilities, that similar fiber types may be primarily responsible for driving mesothelioma risk. This provides further, albeit circumstantial, support for the "amphibole hypothesis" (that amphiboles are primarily responsible for the induction of mesothelioma, even when present as minor contaminants in chrysotile).

Given the importance of these two issues: (1) the relative potencies of chrysotile and the amphiboles and (2) the adequacy of EPA models for predicting the time dependence of disease, limited analysis of raw data from a small number of additional cohorts is warranted. Such recommendations are discussed further in the conclusions to this Chapter (Section 6.4).

6.3.1.2 Comparison with a biologically based model

Definition of the two-stage model. The two-stage model of cancer implemented in this report (Moolgavkar and Luebeck, 1990) was previously described (Section 6.2.1.2).

Table 6-26

Applying the two-stage model to mesothelioma. The 2-stage model was fit to the mesothelioma data using the same general approach applied to the lung cancer data and described earlier (Section 6.2.1.2). Since the background risk of mesothelioma is very small, the first stage mutation rate, v_0, was fixed at zero in these analyses. Also, the death rate for intermediate cells, β_0, was likewise fixed at zero. (This is not expected to affect the range of hazards predicted by the model, since so long as the hazard is small, it is approximately a function of the difference $\alpha - \beta$.). Four situations were modeled:

(1) assuming only the mutation rate of normal cells into intermediate cells is dose-related [$v = v_1 d(t)$, $\alpha = \alpha_0$, $\mu = \mu_0$];

(2) assuming both the mutation rate of normal cells and the proliferation rate of intermediate cells are dose-related [$v = v_1 d(t)$, $\alpha = \alpha_0 + \alpha_1 d(t)$, $\mu = \mu_0$];

(3) assuming both mutation rates are dose-related [$v = v_1 d(t)$, $\alpha = \alpha_0$, $\mu = \mu_0 + \mu_1 d(t)$]; and

(4) assuming that both mutation rates are dose-related and equal on a per-cell basis [$v = \mu X = v_1 d(t)$, $\alpha = \alpha_0$, where $X = 10^7$ is the assumed number of normal cells].

The two-stage model was fit to the mesothelioma data from both Wittenoom and Quebec in a variety of situations. Table 6-27 shows results of fitting the two-stage model to the Wittenoom mesothelioma data assuming either an infinite half-life of internally deposited fibers ($r = 0$) or a ten-year half-life ($r = 0.069$). This Table shows the results of fitting allowing each one of the four parameters α, β, v, and μ individually to be related to internal exposure (Model 1-4) and allowing all four simultaneously to be exposure-related (Models 5,6). The best fit (largest likelihood) using a single exposure-related parameter came from allowing v to depend upon exposure. This was true when either an infinite half-life or a ten-year half-life was assumed. The likelihoods from the two assumed half-lives were similar. The estimated parameters were also similar, except for v_1, which was larger using to ten-year half life in order to compensate for the smaller estimated exposures in this case.

The fit with an infinite half-life allowing all four parameters to be exposure-related (Model 5) did not improve the fit, even though parameter estimates differed considerably. This suggests that the likelihood is quite flat and diverse parameter estimates can provide comparable fits. However, the differences $\alpha_0 - \beta_0$ are nearly constant, which is consistent with the observation by Moolgavkar *et al.* (1988) that in many cases the model depends upon these parameters mainly through their difference.

Table 6-27

Allowing each of the parameters to be exposure-related did significantly improve the fit of the model assuming a ten-year half life over that obtained by assuming any one of the parameters to be exposure-related, based on the improvement in the log-likelihood.

The model assuming an infinite half-life and all four two-stage parameters dose-related predicts that the background hazard increases sharply between age 50 and 60 and reaches a plateau of about $7x10^{-5}$ per year from age 60 onward. This seems somewhat implausible given the low mortality rate for mesothelioma in persons without asbestos exposure. Consequently, this model was refit with the background mesothelioma risk of zero, by assuming both v_0 and μ_0 were fixed at zero (Model 6). This model, although being perhaps more realistic, gave a poorer fit ($p = 0.03$ for infinite half-life and $p=0.08$ for ten-year half-life, based on likelihood ratio test) than the model with the high background.

That the highest likelihoods for the Wittenoom data arise when the mutation rate from normal to intermediate cells (v) is dose related, suggests that asbestos is acting as an initiator for mesothelioma. That the fit improves when either the proliferation rate or the mutation rate of intermediate cells is also allowed to vary with dose suggests that asbestos may also be serving as either a promoter or a late-stage actor for mesothelioma. This contrasts with the two-stage model results for lung cancer, in which having v dose dependent did not improve the fits. Given the apparent limitations of the two-stage model, the interpretation of such results needs to be taken with great caution. However, the implication that asbestos serve primarily as a promoter (or late stage actor) toward lung cancer but also acts as an initiator toward mesothelioma is consistent with inferences from the broader literature (see Section 7.3).

Table 6-28 shows the fit of the two-stage model with an an infinite half-life and without background ($v_0 = \mu_0 = 0$) to the Wittnoom data categorized as to time since end of exposure. The fit of these data to the two-stage model is poor ($P = 0.03$). For comparison purposes the fit of the EPA mesothelioma model to the same data is also provided. The EPA model provides an adequate fit ($p = 0.21$), which is the same as previously indicated (Table 6-24).

Based on this limited exploration of the application of the two-stage model to the Wittenoom data, as well as the Quebec data (not shown), the decision has been reached that this model is probably not suitable for routine use in asbestos risk assessment. There are several reasons for this conclusion. The two-stage model was originally considered because there was some evidence from the literature that the mesothelioma risk did not continue to rise after the end of exposure, as predicted by the EPA model. The hazard function from the two-stage model predicts that risk will eventually fall back to baseline after exposure ceases, and consequently can predict

Table 6-28

this behavior. However, a detailed analysis of the mesothelioma data from both Wittnoom and Quebec indicates that neither demonstrates such behavior (Section 6.3.1.1). In fact, if anything, the EPA model may tend to under-predict the risk at the longest time periods following cessation of exposure (based on the Wittenoom data), although the results with the other two cohorts may not support this observation (see Tables 6-24, 6-25, and 6-26).

Although the two-stage model has been shown to be a useful research tool, some of its features make it less suitable for routine use in risk assessment. The model is complex and would be more difficult to comprehend by stakeholders in an asbestos risk assessment. Because of the numerous parameters in the model, numerical calculations are time-consuming and the results are sometimes problematic. Data are sometimes compatible with a range of possible outcomes under this model (e.g., exposure affecting either the first mutation rate or the cell death rate); currently the mechanism of mesothelioma causation is not well enough understood to permit choice among these possibilities with any degree of confidence, although our findings are not inconsistent with inferences from the literature (see Section 7.3). Moreover, the absence of a single "potency parameter" in the two-stage model would complicate simple comparisons of potency across studies or environments. For these reasons, the decision was reached to not pursue the two-stage model further in this project, but instead to consider simple modifications to the existing EPA model for cases in which this model was not adequate (Section 6.2.1.1).

An advantage of the two-stage model is that, since it models risk as a function of internal dose, it can naturally incorporate effects of fiber clearance. However, we found that, due to the complexity of the model, it was neither particularly useful at predicting fiber half-lives nor distinguishing among assumed half-lives. We also found it possible to develop simpler adaptations to the EPA model that could reasonably address this consideration (Section 6.2.1.1) and found this latter approach more fruitful.

6.3.2 Estimating K_M's from Published Epidemiology Studies

At the time that the Health Effects Update was published (U.S. EPA 1986), four studies were found to provide suitable quantitative data for estimating a value for K_M and six additional studies provide corroborative support for the mesothelioma model applied. Currently, there are 14 published studies with adequate data for deriving an estimate of K_M (including updates to all four of the quantitative studies evaluated in 1986).

The EPA mesothelioma model described at the beginning of Section 6.3 was applied to each of these data sets to obtain study-specific estimates for the mesothelioma risk coefficient, K_M. The resulting set of K_M values are presented in Table 6-12 (which has been previously described, Section 6.2.2**.** In Table 6-12, Columns 9 and 10 list, respectively, the best estimate of each K_M value derived for studies reported in the original 1986 Health Effects Update and the reference for each respective study. Columns 11, 12, and 13 present, respectively: the best-estimates for the K_M values

derived for all of the studies currently available (including studies corresponding to those in the original Health Effects Update); the estimated lower and upper bounds for each K_M value (derived as described in Appendix A); and the reference for the respective study from which the data were obtained. To assure comparability across studies, values for all studies (even those that have not been updated since their inclusion in the 1986 Health Effects Update) were re-derived using the modified procedures described in Appendix A.

The K_M values derived in this study and the corresponding values derived in the original 1986 Health Effects Update are in close agreement, none vary by more than a factor of 2 and none of the differences appear significant (based on a comparison of their relative confidence intervals).

Among the K_M values derived in the current study, the lowest and highest of the best-estimate values differ by a factor of approximately 1400 (excluding the one negative study) and many of the pair-wise comparisons across this spectrum appear significant (because their confidence intervals do not overlap). For example, none of the confidence intervals for the K_M values derived for any of the environments involving exposure to chrysotile overlap the confidence intervals associated with the K_M values derived for either crocidolite mining or asbestos-cement manufacture using mxed fibers at the Ontario plant (Finkelstein 1984). Furthermore, neither of the confidence intervals for the K_M values derived for each of the two sets of chrysotile mines in Quebec (Asbestos and Thetford) overlap the intervals around K_M values for any of the amphibole environments or any of the mixed environments, except the Quebec factory that is associated with the Asbestos mine (Liddell et al. 1997).

The K_M values and the associated confidence bounds derived in the current study are plotted in Figure 6-5. Each exposure environment is plotted along the X-axis of the figure and is labeled with a four-digit code that indicates fiber type (chrysotile, mixed, crocidolite, or tremolite), industry (mining, friction products, asbestos-cement pipe, textiles, insulation manufacturing, or insulation application); and a two-digit numerical value indicating the study from which the data were derived. The same key provided for Figure 6-3 also applies to this figure. In the Figure, the chrysotile studies are grouped on the left, amphibole studies are grouped on the right, and mixed studies are in the middle. Note also that studies conducted in the same facility (generally among highly overlapping cohorts), such as the Dement et al. (1994) and the McDonald et al. (1983a) studies of the same South Carolina textile facility, are combined as a single entry in the Figure. The cohorts from Asbestos Quebec and Thetford are also combined in the Figure.

Figure 6-5

As with the K_L values, comparison of K_M values across the available studies are instructive. Within chrysotile studies alone, lowest and highest K_M values vary by approximately a factor of 15 (again, excluding the negative friction products study), which is minimal variation relative to the spread across the values from all of the studies in the table. Based on the overlap of their confidence intervals, none of these differences appear to be significant.

The K_M values for the two "pure" amphibole studies (crocidolite mining and amosite manufacturing) agree to within a factor of 2 and, with the exception of the value from the Ontario asbestos-cement plant (Study No. 8 in the Figure) and the factory plant associated with the Asbestos, Quebec mines (Study No. 14), the mixed exposures fall in between the high values for the "pure" amphibole exposures and the lower values reported for all of the chrysotile sites. Although the K_M value for the asbestos-cement plant (Study No. 8) appears high, it does not appear to be significantly different than the values from either of the "pure" amphibole studies or values for many of the other mixed exposures (based on the degree of overlap of their respective confidence intervals). The K_M value reported for the factory associated with the Asbestos, Quebec mine (Study No. 14) is the lowest of those reported for mixed exposures, but (again based on the overlap of confidence intervals) it does not appear to differ significantly from values for several of the other mixed exposures nor the highest values among the chrysotile studies.

As with K_L values, the asbestos-cement pipe industry shows the greatest variation in K_M values across all asbestos types, with a range that varies over a factor of 90. Moreover, the difference between the highest and lowest values in this industry may be significant (due to the lack of overlap of their intervals). Within the textile industry, the K_M value for the South Carolina chrysotile plant is only a tenth of the values reported for the two textile plants using mixed fibers, but these differences do not appear to be pairwise significant. The potential sources of variation across all of the K_M values are likely attributable to the same sources of variation identified for the K_L values and previously described in detail (Section 6.22).

6.3.3 Evaluating Effects Associated with the Character of Exposure

To evaluate the effects of fiber size on the K_M values listed in Table 6-12 (in parallel with the manner in which the K_L values were evaluated) K_M values were also adjusted to match them to the improved exposure index defined in Equation 6.7 and the implications of these adjustments were evaluated (in a manner entirely analogous to that described in Section 6.2.4.2). The justification for the development of the improved exposure index is provided in Appendix B.

6.3.3.1 Adjusting K_M's for size

The K_M values were adjusted for size in the same manner described in Section 6.2.4.1 for the K_L values. To accomplish this, the same, published fiber size distributions were matched to the same epidemiology studies (Table 6-14) and the conversions performed as described by Equations 6.4 to 6.6 using the data presented in Table 6-15. The resulting adjusted values, the K_{M^*}'s are listed in Table 6-16.

6.3.3.2 Evaluating the implications of adjusting K_M's for size

To compare the effects of adjusting K_M values for fiber size, the adjusted values (the K_{M^*}'s), are plotted (along with their associated confidence intervals) in Figure 6-6, which exhibits a format identical to that of Figure 6-5. In fact, the formats of Figures 6-3 (unadjusted K_L's), 6-4 (the adjusted, K_{L^*}'s), 6-5 (unadjusted K_M's), and Figure 6-6 (adjusted, K_{M^*}'s) are also designed for direct comparison. The "key" provided for Figure 6-3 is also directly transferable to all of the figures, including Figure 6-6.

Although Figures 6-5 and 6-6 may look similar at first glance, there are several differences. First, the value for study MF14 had to be omitted from Figure 6-6 because no suitable size distribution is available to allow the potency factor from this study to be adjusted. The confidence intervals presented in Figure 6-6 are also larger than those depicted in Figure 6-5. This is because the one's depicted in Figure 6-6 incorporate an additional factor to account for the uncertainty of adjusting for fiber size using paired data from published size distributions. Table 6-17 lists the factors by which the upper bounds are multiplied and lower bounds are divided to derive the confidence intervals depicted in Figure 6-6.

The most important differences between Figures 6-5 and 6-6 are the changes in the relative positions of the central value estimates for the potency factors depicted. Therefore, numerical representations of these changes are provided in Table 6-18.

Table 6-18 presents the magnitude of the spread in the range of original and adjusted K_M values (original and adjusted K_L values are also presented, see Section 6.2.4.2). Such spreads are estimated as the quotient of the maximum and minimum values of each range. As previously indicated, this type of analysis (of necessity) requires that the zero value obtained for the Connecticut friction products plant study (CF4) be omitted. The one study for which no suitable conversion factor could be found for the corresponding K_M, (Study No. MF14) was also omitted.

Figure 6-6

The trends apparent in Table 6-18 that were described for a comparison between K_L and K_{L^*} values are similar but exaggerated between the K_M and K_{M^*} values. Briefly, the spread in values among "pure"fiber types (i.e. chrysotile or amphiboles only) are much smaller than the spread observed over all values (or over data sets that include mixed exposures) and this is true for both the adjusted and unadjusted K_M values. This suggests that chrysotile and the amphiboles exhibit different potencies toward the induction of mesothelioma. Also, the spreads for all of the data sets presented in Table 6-18 (except the one for pure amphiboles, which is already minuscule) are reduced when values are adjusted for fiber size. However, even for adjusted values, the spreads in data sets including mixed exposures are still rather large. As for lung cancer, this implies that the effects of fiber type and fiber size are also confounded for mesothelioma. Therefore, an evaluation similar to that conducted for lung cancer potency factors was also conducted for mesothelioma potency factors to simultaneously address the effects of fiber size and fiber type. The manner in which the evaluation was conducted is described in Section 6.2.4.2.

Table 6-19 presents the results of the analysis in which the K_M estimates are adjusted both for fiber size and for the fraction of the exposures in each environment contributed by amphiboles. As previously described, K_{MA} values are the estimated potencies of pure amphiboles, K_{MA^*}'s are the estimated potency of pure amphiboles adjusted for fiber size, and RPC is the ratio of the potency of pure chrysotile to pure amphibole toward the induction of mesothelioma, in this case (see Section 6.2.4.2). In the analysis, the spread of the range in values for each data set was minimized by optimizing the value for RPC.

That the optimum values for RPC (presented in Column 3 of Table 6-19) are substantially smaller than one for both the unadjusted K_{MA} values and the K_{MA^*} values (which are adjusted for fiber size) suggests that chrysotile is substantially less potent toward the induction of mesothelioma than amphiboles and may be non-potent. However, because Improvement (reduction) in the spread in values for these data sets becomes marginal for values of RPC less than about 1/1000, a conservative estimate suggests that, at most, chrysotile is no more than 1/1000 as potent as amphiboles toward the induction of mesothelioma.

Based on a comparison of the magnitude of the spreads in range for each data set (listed in Column 4), adjusting mesothelioma potency factors for fiber size results in a 30% improvement in agreement across estimated values. Moreover, simultaneously accounting for the effects of fiber type and fiber size results in very effective reconciliation of potency estimates for mesothelioma. Once adjusted in ths manner, the spread in potency estimates across all 10 of the studies available for this analysis is only a factor of 26 (only a little larger than an order of magnitude). This should provide reasonable confidence that a representative value for amphibole potency that might be selected from this range can be applied to new environments to estimate risk.

As with lung cancer, a more sophisticated analysis of mesothelioma potency values was also completed, which incorporates formal consideration of uncertainty and (due to the manner in which the analysis is performed) allows us to include the nominally zero value from the Connecticut friction products plant (Study No. CF4). The details of the analysis are provided in Section 6.2.4.2. Results are provided in Table 6-21.

As with lung cancer, the results of this more formal analysis of mesothelioma potency factors closely parallels the results described in the above analysis. The best estimated values of the relative potency of chrysotile toward mesothelioma lies between 1/250th (0.004) and 1/570th (0.002) of that for the amphiboles and these values are not statistically different from an estimate of zero potency for chrysotile (P = 0.54 for the unadjusted data set and P = 0.72 for the size adjusted data set).

Adjusting the mesothelioma potency factors for fiber size results in an about a 23% improvement in the overall agreement among values (determined by comparing the relative magnitudes of the optimized "σ" estimated for the size adjusted data set (0.6561) and the unadjusted data sets (0.8123), respectively. Thus, even using the relatively crude procedure of adjusting K_M values based on published (rather than study-specific) size distributions, results in moderate improvement in the agreement in values across studies.

6.4 GENERAL CONCLUSIONS FROM HUMAN EPIDEMIOLOGY STUDIES

Results from our evaluation of the available epidemiology studies indicate that:

(1) the results of individual epidemiology studies are uncertain, especially when one considers all of the major potential sources of uncertainty (rather than simply considering the statistical uncertainty associated with the number of deaths, as is traditionally done). However, more robust conclusions can be drawn from an analysis of the set of epidemiology studies taken as a whole than results derived from individual studies;

(2) by adjusting for fiber size and fiber type, the existing database of studies can be reconciled adequately to reasonably support risk assessment;

(3) the procedures recommended as a result of our analysis offer substantial improvement over EPA's current approach to evaluating asbestos-related risks;

(4) while there is some indication that the existing EPA models for lung cancer and, potentially, mesothelioma may not entirely reflect the time-dependence of disease at long times following cessation of exposure, such effects appear to be modest so that they are unlikely to adversely affect the proposed approach. Prudence dictates, however, that limited additional study may be warranted to adequately dismiss related concerns; and

(5) results from our review of the supplemental literature provide additional support for the approach recommended in this chapter and indicate additional, specific modifications that (if supported by limited additional study) could result in substantial improvement even over the approach currently recommended, which (in turn) provides substantial improvement over the current approach.

More detailed conclusions and recommendations are described below.

Conclusions and Recommendations For Lung Cancer

Without adjustments, the K_L values estimated from the 18 existing studies vary by a factor of 90 and pairwise differences between several individual studies are likely significant (based on a comparison of their associated confidence intervals). By simultaneously adjusting these values for fiber size and type, variation across the 16 studies (for which data are available to make the required adjustments) is reduced to a factor of about 60.

Especially given the crude manner available for performing size adjustments coupled with the very consistent picture that such adjustments improve matters and that there is a strong theoretical basis for expecting that such adjustments should improve cross-study comparison or extrapolation, we believe that such adjustments increase overall confidence in cross-study comparison/extrapolation. We therefore recommend their use.

The maximum and minimum values driving the factor of 60 come from cohorts of South Carolina textile workers and Quebec miners, respectively, and the difference in the lung cancer potency estimated between these studies has long been the subject of much attention. A detailed evaluation of the studies addressing this difference, the results of our analysis of the overall epidemiology literature, and implications from the broader literature, indicate that the most likely cause of the difference between these studies is the relative distribution of fiber sizes in the two study environments. It is therefore likely that the variation between these studies can be further reduced by implementing one or a combination of the following:

- deriving improved characterizations of the exposures experienced by cohort members in each, respective environment based on study-specific size distributions (instead of relying on the cruder use of published distributions, as currently required);

- deriving improved characterization of the exposures experienced by cohort members in each, respective environment based on improved analysis of relevant material (instead of relying on the existing, published distributions, which are insufficiently detailed to capture all of the biologically-relevant aspects of size distributions);

- from a selected subset of key studies, developing the improved characterization data required to allow the existing lung cancer potency factors to be adjusted to an exposure index that is even closer to an optimized index than the one recommended in this document;

- procedures for accomplishing some or all of the these objectives are described below.

Importantly, the exposure index recommended in this document (and used throughout this analysis), while not perfect, when coupled with the recommended adjustments for fiber type, already provides substantial improvement over EPA's current approach to evaluating asbestos-related risks. This is evident, for example, if one compares certain values of the variance (σ) provided in Table 6-21. Because, under the current approach, chrysotile and amphiboles are considered equipotent and lung cancer and mesothelioma risks are combined, the overall variance estimated for the unadjusted K_M values with RPC =1 (1.817) should be compared with the variance estimated for adjusted K_{M^*} values with RPC optimized (0.6561), which represents the recommended approach. Thus, the new approach reduces variance by approximately a factor of three over the current approach. Actually, the improvement is even larger because the K_M values employed in our analysis include a greater number of studies than available to the U.S. EPA in 1986. Therefore, despite our recommendations below to conduct limited, additional study that may lead to further improvements, there is no reason not to implement the recommendations from our current analysis now.

Although the EPA lung cancer model appears to adequately describe the time dependence of disease for amphiboles, it may not adequately describe risks for chrysotile at long times following cessation of exposure. In contrast to predictions from the model (potentially due to the observed, lower biodurability of chrysotile), lung cancer risks from chrysotile decrease with time following cessation of exposure. Thus, if the model is applied to any new site to predict risks, if anything, risk estimates will be conservative. However, particularly for studies with long followup times after cessation of exposure, the K_L's estimated from existing studies (using the EPA model) may be underestimated. Importantly, these conclusions are based on raw observations from only one chrysotile and one amphibole study. Thus, it may be prudent to evaluate raw data from a minimum of one additional chrysotile study and one additional amphibole study to confirm that such observations are indeed general. However, it is likely that these time-dependent effects are relatively small.

Conclusions and Recommendations For Mesothelioma

Without adjustments, the K_M values estimated from the 12 existing studies vary by more than a factor of 1000 and pairwise differences between several individual studies are likely significant (based on a comparison of their associated confidence intervals). By simultaneously adjusting these values for fiber size and type, variation across the 11 studies (for which data are available to make the required adjustments) is reduced to a

factor of about 26. Given that this is little larger than an order of magnitude, it appears that we have essentially reconciled the mesothelioma studies.

Although the EPA mesothelioma model appears to adequately describe the time dependence of disease in general, there was some indication that it may under estimate risks at long times following cessation of exposure for amphiboles. Therefore, as part of the analysis recommended for further testing the time dependence of the lung cancer model, it may also be prudent to further evaluate the behavior of the mesothelioma model.

Conclusions and Recommendations for Risk Assessment

Based on our analysis, we recommend the following.

(1) Asbestos concentrations should be analyzed for structures that correspond to the exposure index defined in Equation 6.7. Thus, count only structures longer than 5 μm and thinner than 0.5 μm with structures longer than 10 μm weighted as indicated in Equation 6.7. Further, count both parent fibers and bundles and fibers and bundles that are components of more complex structures, but that individually satisfy the above-defined dimensional criteria. Importantly, analysis needs to be performed by TEM following preparation by a direct-transfer procedure.

(2) When mixed, the individual contributions from chrysotile and the combined amphiboles to any particular exposure need to be separately delineated and, because amphibole exposures are the primary drivers, the analytical sensitivity required for each particular study should be set based on amphiboles.

(3) Combine such counts with the matched potency factors for lung cancer and mesothelioma described in Tables 6-29 or 6-30 below using the appropriate EPA model for each disease.

Based on our analysis, the optimized potency coefficients that are adjusted for size (so that they are appropriately matched to the exposure index defined above) are obtained from Table 6-21 and reproduced here:

Table 6-29:
Optimized Risk Coefficients
for Pure Fiber Types

Fiber Type	K_{L^*} x 100	K_{M^*} x 10^8
Chrysotile	0.85	0.05
Amphiboles	4.5	30

In keeping with the tradition of incorporating conservative estimates to minimize the chance of under-estimating risks, conservative estimates for the potency factors listed in Table 6-29 are derived by up-adjusting the amphibole potency values for both lung cancer and mesothelioma so that they match the largest value from the set of available studies and adjusting the chrysotile values proportionally. Results from this calculation are presented in Table 6-30.

Table 6-30:
Conservative Risk Coefficients
for Pure Fiber Types

Fiber Type	K_{L^*} x 100	K_{M^*} x 10^8
Chrysotile	3.0	0.1
Amphiboles	15	50

We leave it as an option for deciding which values to employ. Interestingly, however, due to the great degree of reconciliation among the disparate values for the potency estimates already achieved in this document, the ratio of the conservative and optimum K_{L^*} estimates is only a little larger than a factor of 3 while the conservative and optimum K_{M^*} values vary by less than a factor of 2.

Recommendations for Limited, Further Study

The two major objectives identified above for further study are:

(1) to expand the test of the ability of the current EPA models to adequately track the time-dependence of disease; and

(2) to develop the supporting data needed to define adjustments for potency factors that will allow them to be used with an exposure index that even more closely captures the criteria that determine biological activity (see Section 7.5). Among other things, this may ultimately provide the data allowing complete reconciliation of the potency factors derived for Quebec miners and South Carolina textile workers, one of the major outstanding issues identified among asbestos researchers.

The first of the above objectives requires that we gain access to raw data from a small number of selected, additional epidemiology studies. The best candidate studies include: (for chrysotile) the lung cancer data from Quebec (best) or, potentially, from the New Orleans asbestos-cement pipe plant studied by Hughes et al. For amphiboles, the best candidate studies include: the lung cancer and *newest* mesothelioma data

from Libby (best), or, potentially the lung cancer and mesothelioma data from the Paterson, New Jersey insulation manufacturing plant studied by Seidman. The possibility of obtaining some or all of these data sets needs to be further explored.

The second of the above objectives requires more detailed size characterization data for the environments of interest. Although archived air samples do not appear to be available from any of the study locations of interest, we believe that suitable data can be developed from appropriate bulk samples. Thus, for example, it would be useful to obtain samples of the raw ore from Libby, Wittenoom, and Quebec and the textile, asbestos-cement pipe, and friction-product grade products from Quebec. We have already approached individuals who can provide access to these materials and they have all expressed interest in collaborating.

Results from our review of the supporting literature suggest that the optimum cutoff for increased potency occurs at a length that is closer to 20 µm than10 µm, (the latter of which is the cutoff in the exposure index provided in this study). Data do not currently exist to improve on this latter cutoff. However, provided that study-specific size distribution data could be obtained as indicated above, with the appropriate analyses, it will be possible to develop the size distributions necessary to evaluate a range of considerations including:

- delineation of size fractions among individual length categories out to lengths as long as 30 or 40 µm;
- determination of the relative presence and importance of cleavage fragments (of non-biologically relevant sizes) in mine ores vs. finished fibers; and
- the relative fraction of fibrous material vs. non-fibrous particles in the various exposure dusts of interest.